EUKARYOTIC CELL, Apr. 2007, p. 571–583 Vol. 6, No. 4
1535-9778/07/$08.00+0 doi:10.1128/EC.00026-07

MINIREVIEW

Mechanisms Regulating the Protein Kinases of *Saccharomyces cerevisiae*[▽]

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Reversible protein phosphorylation is a ubiquitous post-translational modification in all eukaryotes. It is critically involved in the regulation of nearly all cellular processes and signaling pathways. Protein kinases, the enzymes that catalyze the phosphotransfer reaction, constitute one of the largest protein families, accounting for approximately 2% of the genes in any given eukaryotic genome (122). Few of these kinases are constitutively active; unregulated activity would be deleterious or lethal to cells in the cases of most protein kinases. Cells have thus developed a variety of finely tuned mechanisms to precisely control the activities of these enzymes.

We aim here to characterize the regulatory mechanisms governing the activities of protein kinases in *Saccharomyces cerevisiae* on a genome-wide scale. We do not attempt to review comprehensively the substrates, target sequences, or downstream effects of these kinases. Using yeast as a model system to analyze the regulation of protein kinases on a global scale has advantages. Yeast expresses a limited number of protein kinases relative to metazoans, and the regulation of most yeast kinases has been characterized to some extent and in some cases in exquisite detail. However, the relative simplicity of the yeast kinase collection also presents a limitation: entire families of protein kinases found in other eukaryotes (for example, the receptor- and Src-like tyrosine kinases present in metazoans) are not represented in yeast (122). Nonetheless, reviewing the regulatory paradigms of kinases in yeast is a feasible and illustrative task.

Using yeast as a model, the information reviewed herein suggests that organisms utilize a finite number of regulatory paradigms in controlling their complement of kinases. In fact, this is very much a story of recurrent themes, with similar modes of regulation arising in disparate kinase families. While a cadre of regulatory motifs can be found controlling the activities of constituent members of nearly all evolutionary families of protein kinases, distinct patterns are readily apparent. For example, activating interactions with partner proteins (e.g., calmodulin, Cdc42, and cyclins) and phosphorylation within and outside the activation loop are common regulatory paradigms. Knowledge of regulatory motifs common to specific protein kinase families can be instructive in guiding experiments intended to ascertain the regulation of related, uncharacterized kinases.

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▽ Published ahead of print on 2 March 2007.

NAMES, FAMILIES, AND PHYLOGENY

The enzymes whose mechanisms of regulation are reviewed here are those phosphotransferases that catalyze the transfer of the gamma phosphate from a nucleoside triphosphate (usually ATP) to the hydroxyl groups present in the serine, threonine, and tyrosine side chains of proteins. The yeast genome encodes 117 protein kinases in the superfamily of eukaryotic protein kinases (ePKs) and an additional 10 atypical kinases. Four atypical protein kinases show sequence similarity to phosphoinositide kinases (Tor1, Tor2, Tec1, and Mec1) but are known to phosphorylate proteins; two are related to microbial histidine kinase two-component signal transducers (Sln2 and Ypd1), and though they fail to meet our definition of a protein kinase, their function in signal transduction merits inclusion in this review; two (Pkp1 and YGL059W) are in the pyruvate dehydrogenase kinase (PDHK) family (96); two (Rio1 and Rio2) are in the RIO (right open reading frame) family of protein kinases (100). An additional six yeast proteins that have been classified as kinases will not be reviewed, either because the annotation (13) is now known to be incorrect (as in the case of Twf1) or because there is no experimental evidence to indicate that these proteins catalyze a phosphotransfer reaction (Abc1, YLR253W, YPL109C, Tra1, and Taf1).

Hunter and Plowman (79) were the first to analyze the complete set of yeast protein kinases in *Saccharomyces cerevisiae*. In the 10 years since their publication, many of the hypothetical protein kinases that were encoded by uncharacterized open reading frames have been studied and named. Similarly, some kinases have had their names changed for a variety of reasons. In the Hunter and Plowman study, an unrooted dendrogram of 112 yeast kinase domains was constructed using a protein sequence parsimony method (79). We show here a revised version of this dendrogram that has been updated to contain the names currently used for these enzymes (Fig. 1). Thirty-one kinases (27%) have been named or renamed; only 10 remain as kinases encoded by uncharacterized open reading frames. Also in the intervening years, complete genomic sequence data from other eukaryotes have allowed comparison of kinase families across species (122). The study of Manning et al. (122) makes clear that *S. cerevisiae* completely lacks some families of protein kinases, notably the receptor- and Src-like tyrosine kinases, and contains others that appear in other fungi but are not present in metazoans. More sophisticated analyses of protein kinase phylogeny using hidden Markov models, PSI-BLAST, and homology-based gene predictions have been used to classify the groups, families, and subfamilies of eukaryotic kinases (122). We have used this more recent analysis as the

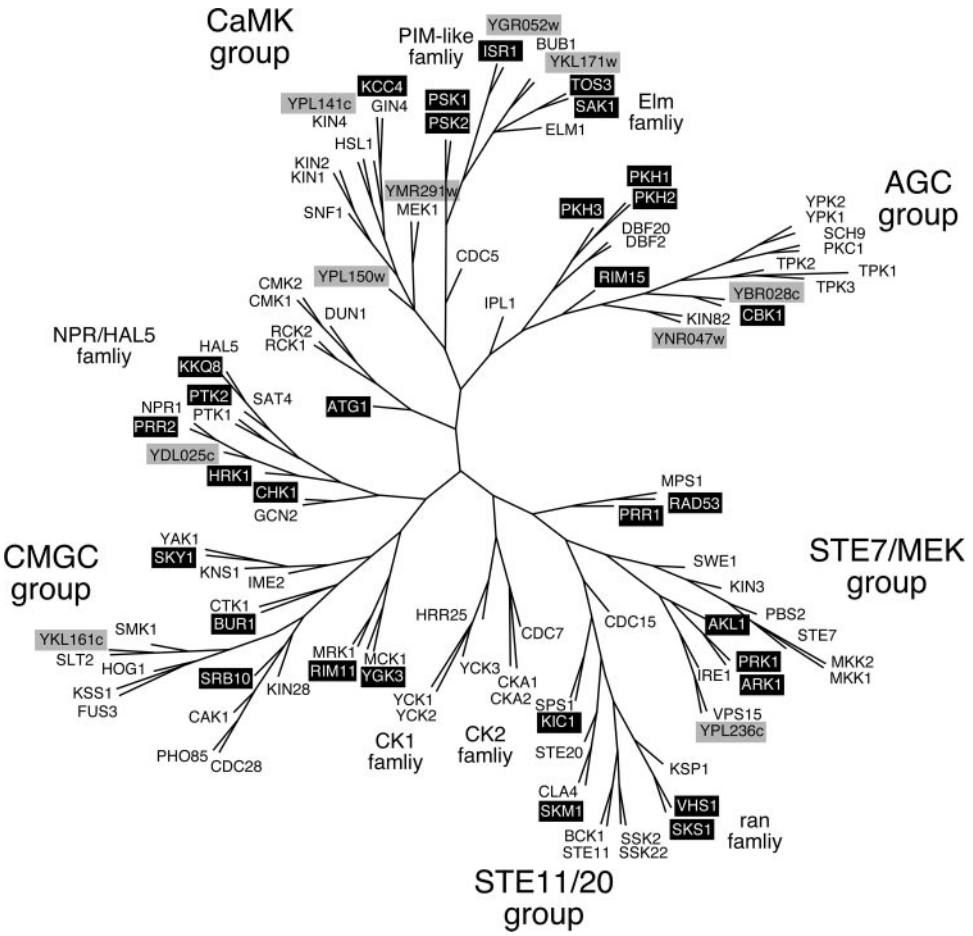

FIG. 1. Unrooted dendrogram of 112 protein kinases of *Saccharomyces cerevisiae*. Kinases that have been named or renamed since this dendrogram was first published (79) are shown in white text over black rectangles. Kinases that remain uncharacterized are shown in black text over gray rectangles. The major groups and families of protein kinases are shown in larger text. Not shown in this dendrogram are Alk1, Alk2, Bud32, Iks1, and Scy1. (Modified from Fig. 1 of reference 79 with permission of the publisher.).

source of our classification of the yeast kinases. Clearly, the present study has led to a reclassification of some of the yeast protein kinases. The discerning reader will note that the classification of some kinases in Tables 1 and 2 may not agree with their positions in the earlier dendrogram (Fig. 1). We do not attempt to resolve these few discrepancies. The focus of this review is not the classification of kinases but rather their mechanisms of regulation.

MECHANISMS OF KINASE REGULATION

We have organized what is known about the regulation of protein kinases in *Saccharomyces cerevisiae* in two different fashions. In Table 1, the kinases are sorted by phylogenetic group, family, and subfamily. The regulatory mechanism(s) for each kinase is shown along with the appropriate citation(s). Table 2 "plots" the regulatory mechanism by phylogenetic group in a manner that allows visualization of the distribution of mechanisms controlling catalytic activity among the evolutionary groups. Every kinase can be found in both tables. The mechanisms listed in Table 1 are shown as abbreviations based on the schema in Table 2. For instance, activation loop autophosphorylation is shown in Table 1 as A1. The information included in Tables 1 and 2 reflects only that which has been specifically published regarding each yeast kinase. For the data in Tables 1 and 2, we have made no inferences from what is known about the regulation of related kinases in yeast or in other species. We have attempted to create a snapshot of the state of knowledge in the field as it stands. Our knowledge of protein kinase regulation is itself an evolving entity. Clearly, what is currently documented about any given kinase is not all that will ever be known about that particular kinase. Similarly, the mechanisms regulating uncharacterized or poorly characterized protein kinases will one day be uncovered.

The mechanisms regulating the activities of protein kinases in *Saccharomyces cerevisiae* can be divided into seven major categories: phosphorylation within the activation loop, phosphorylation outside the activation loop, dephosphorylation, protein binding, binding of nonprotein ligands, protein accumulation, and subcellular localization. Of these, several can be further divided into subcategories. A few kinases appear to be unregulated with constitutive activity (for example, Cak1), while many others (55 kinases) are regulated in complex manners, involving more than one regulatory modality. For exam-

TABLE 1. Mechanisms of kinase regulation[a]

Gene	ORF	Group	Family	Subfamily	Mechanism(s) of regulation[b] (reference[s] and/or source)
Sch9	YHR205W	AGC	AKT		A2 (180)
Ypk1	YKL126W	AGC	AKT		A2 (26, 37, 180)
Ypk2	YMR104C	AGC	AKT		A2 (26, 37, 180)
Cbk1	YNL161W	AGC	NDR		D1 (232)
Rim15	YFL033C	AGC	NDR		B2 (175, 212, 229); G (212, 229)
Dbf2	YGR092W	AGC	NDR		A2 (120); D1 (120); G (223)
Dbf20	YPR111W	AGC	NDR		U
Pkh1	YDR490C	AGC	PDK1		E1 (112)
Pkh2	YOL100W	AGC	PDK1		E1 (112)
Pkh3	YDR466W	AGC	PDK1		U
Tpk1	YJL164C	AGC	PKA		D2 (87, 174); E1 (87)
Tpk2	YPL203W	AGC	PKA		D2 (87, 174); E1 (87)
Tpk3	YKL166C	AGC	PKA		D2 (87, 174); E1 (87)
Pkc1	YBL105C	AGC	PKC		A2 (80, 180); D1 (91); E1 (91); G (38)
	YBR028C	AGC	RSK	p70	U
Kin82	YCR091W	AGC	RSK		U
	YNR047W	AGC	RSK		U
Cmk1	YFR014C	CaMK	CaMK1		D1 (152, 159); E1 (152, 159)
Cmk2	YOL016C	CaMK	CaMK1		D1 (152, 159); E1 (152, 159)
Rck1	YGL158W	CaMK	CaMK1		U
Rck2	YLR248W	CaMK	CaMK1		B1 (17, 216); D2 (134); F (173, 211)
Snf1	YDR477W	CaMK	CaMKL	AMPK	A2 (76, 130, 144, 208); C2 (130); D1 (191); D2 (86, 104); G (74, 75, 221)
Chk1	YBR274W	CaMK	CaMKL	CHK1	B1 (3)
Gin4	YDR507C	CaMK	CaMKL	NMR	A2 (K. Elbing and M. C. Schmidt, unpublished data); B1 (7); D1 (11, 41, 66, 142); G (155)
Hsl1	YKL101W	CaMK	CaMKL	NMR	A2 (K. Elbing and M. C. Schmidt, unpublished data); B2 (31); D1 (11, 66); D2 (70); F (25); G (31, 138)
Kcc4	YCL024W	CaMK	CaMKL	NMR	A2 (K. Elbing and M. C. Schmidt, unpublished data); D1 (11, 66, 154); G (154)
Kin1	YDR122W	CaMK	CaMKL	Kin1	D1 (45); D2 (45)
Kin2	YLR096W	CaMK	CaMKL	Kin1	D1 (45); D2 (45)
Kin4	YOR233W	CaMK	CaMKL	Kin4	G (35)
	YPL141C	CaMK	CaMKL	Kin4	U
	YPL150W	CaMK	CaMKL	MARK	U
Psk1	YAL017W	CaMK	CaMKL	PASK	D1 (185)
Psk2	YOL045W	CaMK	CaMKL	PASK	D1 (185)
	YKL171W	CaMK	Unique		U
Mek1	YOR351C	CaMK	Unique		D1 (148, 225)
Prr1	YKL116C	CaMK	Unique		U
	YMR291W	CaMK	Unique		U
Dun1	YDL101C	CaMK	RAD53		A2 (28); B1 (12); D1 (12, 103)
Rad53	YPL153C	CaMK	RAD53		A1 (117); B1 (103)
Hrr25	YPL204W	CK1	CK1	CK1-D	D1 (162); G (219)
Yck2	YNL154C	CK1	CK1	CK1-G	C1 (60); G (9, 219)
Yck3	YER123W	CK1	CK1	CK1-G	G (206)
Yck1	YHR135C	CK1	CK1	CK1-G	C1 (60); D1 (139); G (219)
Cdc28	YBR160W	CMGC	CDK	CDC2	A2 (49, 183); B2 (19); C1 (110, 184); C2 (29); D1 (39, 63, 65, 207); D2 (135, 151); G (136)
Pho85	YPL031C	CMGC	CDK	CDK5	B1 (147); D1 (51, 77, 132, 133, 228); D2 (78, 192)
Kin28	YDL108W	CMGC	CDK	CDK7	A2 (50, 94); D1 (93, 210)
Srb10	YPL042C	CMGC	CDK	CDK8	D1 (98, 108)
Ctk1	YKL139W	CMGC	CDK	CRK7	A2 (157); D1 (73, 203)
Cak1	YFL029C	CMGC	CDK		F (54, 224); H (89, 209)
Bur1	YPR161C	CMGC	CDK		A2 (242); D1 (241)
Cka1	YIL035C	CMGC	CK2		D1 (15, 97)
Cka2	YOR061W	CMGC	CK2		D1 (97)
Kns1	YLL019C	CMGC	CLK		H (101)
Yak1	YJL141C	CMGC	DYRK	YAK	A1 (92); B2 (125, 245); F (200); G (125, 140)
Mck1	YNL307C	CMGC	GSK		A1 (109)
Mrk1	YDL079C	CMGC	GSK		U
Rim11	YMR139W	CMGC	GSK		A1 (247)
Ygk3	YOL128C	CMGC	GSK		U
Fus3	YBL016W	CMGC	MAPK	ERK	A2 (47, 62); C2 (246); D1 (30, 57, 95, 124); G (18, 30, 169)
Hog1	YLR113W	CMGC	MAPK	ERK	A2 (23); C2 (123, 128, 230, 239, 243); G (55)
Kss1	YGR040W	CMGC	MAPK	ERK	A2 (62, 116)
Slt2	YHR030C	CMGC	MAPK	ERK	A2 (127); C2 (32, 56, 69, 129); D1 (137); G (220)
Smk1	YPR054W	CMGC	MAPK	ERK	A2 (187); F (163)
	YKL161C	CMGC	MAPK	ERK	U
Ime2	YJL106W	CMGC	RCK		A1 (189); A2 (188); D2 (43); F (22, 24, 68, 168)
Sky1	YMR216C	CMGC	SRPK		H (150)
Ipl1	YPL209C	Other	AUR		A1 (52); G (16)
Bub1	YGR188C	Other	BUB		D1 (179); G (64, 179)
Bud32	YGR262C	Other	Bud32		A1 (53)
Elm1	YKL048C	Other	CaMKK	ELM	D1 (183); G (21)
Sak1	YER129W	Other	CaMKK	ELM	D1 (183)
Tos3	YGL179C	Other	CaMKK	ELM	D1 (183)
Cdc7	YDL017W	Other	CDC7		D1 (44, 156)
Npr1	YNL183C	Other	HAL		B2 (190); C1 (82)
Ptk1	YKL198C	Other	HAL		U
Hrk1	YOR267C	Other	HAL		U

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TABLE 1—*Continued*

Gene	ORF	Group	Family	Subfamily	Mechanism(s) of regulation[b] (reference[s] and/or source)
Hal5	YJL165C	Other	HAL		U
Kkq8	YKL168C	Other	HAL		U
Prr2	YDL214C	Other	HAL		U
Ptk2	YJR059W	Other	HAL		U
Sat4	YCR008W	Other	HAL		U
	YDL025C	Other	HAL		U
Alk1	YGL021W	Other	Haspin		F (146)
Alk2	YBL009W	Other	Haspin		F (146)
Iks1	YJL057C	Other	IKS		U
Ire1	YHR079C	Other	IRE		A1 (197); C2 (67); D1 (197) D2 (153)
Akl1	YBR059C	Other	NAK		U
Ark1	YNL020C	Other	NAK		G (33)
Prk1	YIL095W	Other	NAK		G (33)
	YPL236C	Other	NAK		U
Kin3	YAR018C	Other	NEK		U
Isr1	YPR106W	Other	Unique		U
	YGR052W	Other	Unique		U
Gcn2	YDR283C	Other	PEK	GCN2	D1 (42, 61); D2 (170); E1 (171)
Cdc5	YMR001C	Other	PLK		A2 (141); G (6, 201)
Sks1	YPL026C	Other	RAN		U
Ksp1	YHR082C	Other	RAN		G (58)
Vhs1	YDR247W	Other	RAN		U
Scy1	YGL083W	Other	SCY1		U
Mps1	YDL028C	Other	TTK		B1 (83); D1 (193); F (83)
Atg1	YGL180W	Other	ULK		B1 (227); B2 (90, 227); D1 (90)
Vps15	YBR097W	Other	VPS15		D1 (199, 202)
Swe1	YJL187C	Other	WEE		B1 (72); B2 (6, 186); D2 (198); F (6, 88, 131, 186)
Bck1	YJL095W	STE	STE11		A2 (36, 102)
Ssk2	YNR031C	STE	STE11		A1 (164); D1 (164); G (244)
Ssk22	YCR073C	STE	STE11		A1 (164); D1 (164)
Ste11	YLR362W	STE	STE11		A2 (45, 165); D1 (1, 71, 167, 236); F (48); G (218, 235)
Cdc15	YAR019C	STE	STE20	MST	C1 (84, 240); D1 (5, 178); D2 (10); G (27, 223)
Cla4	YNL298W	STE	STE20	PAK	D1 (14, 20, 217); D2 (126); E1 (233); G (186)
Skm1	YOL113W	STE	STE20	PAK	D2 (126)
Ste20	YHL007C	STE	STE20	PAK	B1 (237); D1 (8, 99, 105, 161, 234); D2 (59, 99); G (4, 8, 237)
Kic1	YHR102W	STE	STE20	YSK	D1 (205)
Sps1	YDR523C	STE	STE20	YSK	F (160)
Mkk1	YOR231W	STE	STE7		A2 (81)
Mkk2	YPL140C	STE	STE7		A2 (81)
Pbs2	YJL128C	STE	STE7		A2 (118); D1 (71, 118, 165, 215); G (172, 177)
Ste7	YDL159W	STE	STE7		A2 (145); D1 (194); F (226)
Sln1	YIL147C	Atypical	HisK		B1 (166); E1 (119, 214)
Ypd1	YDL235C	Atypical	HCPT		B1 (166); G (115)
	YGL059W	Atypical	PDHK		U
Pkp1	YIL042C	Atypical	PDHK		U
Tel1	YBL088C	Atypical	PIKK	ATM	G (111, 213)
Mec1	YBR136W	Atypical	PIKK	ATR	D1 (143, 182); G (213)
Tor1	YJR066W	Atypical	PIKK	FRAP	D1 (176); G (107, 231)
Tor2	YKL203C	Atypical	PIKK	FRAP	D1 (238); G (231)
Rio1	YOR119C	Atypical	RIO	RIO1	U
Rio2	YNL207W	Atypical	RIO	RIO2	U

[a] AKT, kinase from the AKT8 retrovirus; AMPK, AMP-activated protein kinase; ATM, ataxia-telangiectasia mutated; ATR, ATM-Rad3 related; AUR, aurora; BUB, budding uninhibited by benomyl; CaMKK, CaMK kinase; CaMKL, CaMK like; CK1, casein kinase 1; CK1-D, casein kinase 1 delta; CK1-G, casein kinase 1 gamma; CK2, casein kinase 2; CLK, CDK-like kinase; ELM, elongated morphology; ERK, extracellular signal-regulated kinase; FRAP, FKBP-rapamycin associated protein; HAL, halotolerance; Haspin, haploid germ cell-specific nuclear protein kinase; HCPT, histidine-containing phosphotransmitter; HisK, histidine kinase; IRE, inositol required; MARK, microtubule affinity-regulating kinase; MST, mammalian STE20-like protein kinase; NAK, NF-κ B-activating kinase; NDR, nuclear Dbf2 related; NEK, NIMA-related kinase; NMR, NIM related; PEK, pancreatic eIF-2a kinase; PIKK, phosphoinositide-3-kinase-related protein kinase; PLK, polo-like kinase; RAN, RAN (nuclear import/export) related; RCK, radiation sensitivity-complementing kinase; RSK, ribosomal S6 kinase; SRPK, serine/arginine-rich protein-specific kinase; TTK, dual-specificity protein kinase; ULK, UNC-51-like kinase; WEE, *Schizosaccharomyces pombe* wee1 homolog; YAK, yet another kinase.
[b] See Table 2 for mechanism abbreviations.

ple, Cdc28 is subject to at least seven distinct mechanisms for its regulation.

Activation loop phosphorylation. One of the most well-characterized mechanisms by which protein kinases are activated is phosphorylation of the activation loop (also called the T loop), the flexible polypeptide segment that connects the N and C lobes of the kinase domain (149). Activation loops are typically 20 to 35 residues long and bounded by the conserved residues DFG at the segment's N terminus and APE at the C terminus. The sequence of the loop itself is less well conserved but often contains one or two conserved phosphorylatable residues. The conformation of the activation loop relative to the kinase domain changes with its phosphorylation status. The conformational shift controls the activity state of the kinase by either relieving the steric hindrance of the substrates to the active site, aligning the catalytic residues, or both (2, 149).

Two alignments of the activation loops from 58 yeast kinases are shown in Fig. 2. The kinases are arranged by group. The top alignment contains representatives from four of the six groups of ePKs present in yeast. The position of the conserved phosphorylated threonine residue is indicated. The lower alignment shows selected members of the CMGC group (a kinase family that includes cyclin-dependent kinases [CDKs], mitogen-activated protein kinases [MAPKs], glycogen synthase kinases [GSKs], and CDK-like kinases), including the MAPKs and CDKs that are phosphorylated on threonine, tyrosine, or

TABLE 2. Kinase regulatory themes

Regulatory mechanism[a]	Theme(s) for indicated kinase group						
	AGC	CaMK	CMGC	STE	CK1[b]	Other	Atypical
A. Activation loop phosphorylation							
1. Autophosphorylation		Rad53	Mck1, Ime2, Rim11, Yak1	Ssk2, Ssk22		Bud32, Ipl1, Ire1	
2. Upstream kinase	Dbf2, Pkc1, Sch9, Ypk1, Ypk2	Dun1, Gin4, Hsl1, Kcc4, Snf1	Bur1, Cdc28, Ctk1, Fus3, Hog1, Ime2, Kin28, Kss1, Slt2, Smk1	Bck1, Ste11, Mkk1, Mkk2, Pbs2, Ste7		Cdc5	
B. Phosphorylation outside loop							
1. Activating		Chk1, Dun1, Gin4, Rad53, Rck2	Pho85	Ste20		Atg1, Mps1, Swe1	Sln1, Ypd1
2. Inactivating	Rim15	Hsl1	Cdc28, Yak1			Atg1, Npr1, Swe1	
C. Dephosphorylation							
1. Activating			Cdc28,	Cdc15	Yck1, Yck2	Npr1	
2. Inactivating		Snf1	Cdc28, Fus3, Hog1, Slt2			Ire1	
D. Protein binding							
1. Activating	Cbk1, Dbf2, Pkc1	Cmk1, Cmk2, Dun1, Gin4, Hsl1, Kcc4, Kin1, Kin2, Mek1, Psk1, Psk2, Snf1	Bur1, Cdc28, Cka1, Cak2, Ctk1, Fus3, Kin28, Pho85, Slt2, Srb10	Cdc15, Cla4, Kic1, Pbs2, Ssk2, Ssk22, Ste7, Ste11, Ste20	Hrr25, Yck1	Atg1, Bub1, Cdc7, Elm1, Gcn2, Ire1, Mps1, Sak1, Tos3, Vps15	Mec1, Tor1, Tor2
2. Inactivating	Tpk1, Tpk2, Tpk3	Hsl1, Kin1, Kin2, Rck2, Snf1	Cdc28, Ime2, Pho85	Cdc15, Cla4, Skm1, Ste20		Gcn2, Ire1, Swe1	
E. Binding nonprotein ligands							
1. Activating	Pkc1, Pkh1, Pkh2, Tpk1, Tpk2, Tpk3	Cmk1, Cmk2		Cla4		Gcn2	Sln1
2. Inactivating							
F. Accumulation		Hsl1, Rck2	Cak1, Ime2, Smk1, Yak1	Ste7, Ste11, Sps1		Alk1, Alk2, Mps1, Swe1	
G. Localization	Dbf2, Pkc1, Rim15	Gin4, Hsl1, Kcc4, Kin4, Snf1	Cdc28, Fus3, Hog1, Slt2, Yak1	Cdc15, Cla4, Pbs2, Ssk2, Ste11, Ste20	Hrr25, Yck1, Yck2, Yck3	Ark1, Bub1, Cdc5, Elm1, Ipl1, Ksp1, Prk1	Mec1, Tel1, Tor1, Tor2, Ypd1
H. Constitutive			Cak1, Kns1, Sky1				
U. Unknown	Dbf20, Kin82, Pkh3, YBR028C, YNR047W	Prr1, Rck1, Ygk3, YKL171W, YMR291W, YPL141C, YPL150W	Mrk1, Ygk3, YKL161C			Akl1, Hal5, Hrk1, Kin3, Kkq8, Iks1, Isr1, Prr2, Ptk1, Ptk2, Sat4, Scy1, Sks1, Vhs1, YDL025C, YGR052W, YPL236C	Pkp1, Rio1, Rio2, YGL059W

[a] The letters and numbers designating the regulatory mechanisms are used in Table 1.
[b] CK1, casein kinase 1.

both residues and contain a slightly different spacing of the phosphorylated site(s). Only 37 of 117 yeast protein kinases in the ePK family are currently known to be activated by phosphorylation of one or more critical residues within the activation loop (Table 2). However, sequence conservation suggests that many more kinases may ultimately be added to this list. Examination of the alignment of these activation loop sequences allows several predictions to be made. First, many kinases lack the conserved phosphorylatable residues in their loops and are probably not regulated by activation loop phosphorylation. For instance, the yeast calcium/calmodulin-activated kinases (CaMKs) (Cmk1 and Cmk2) lack the conserved

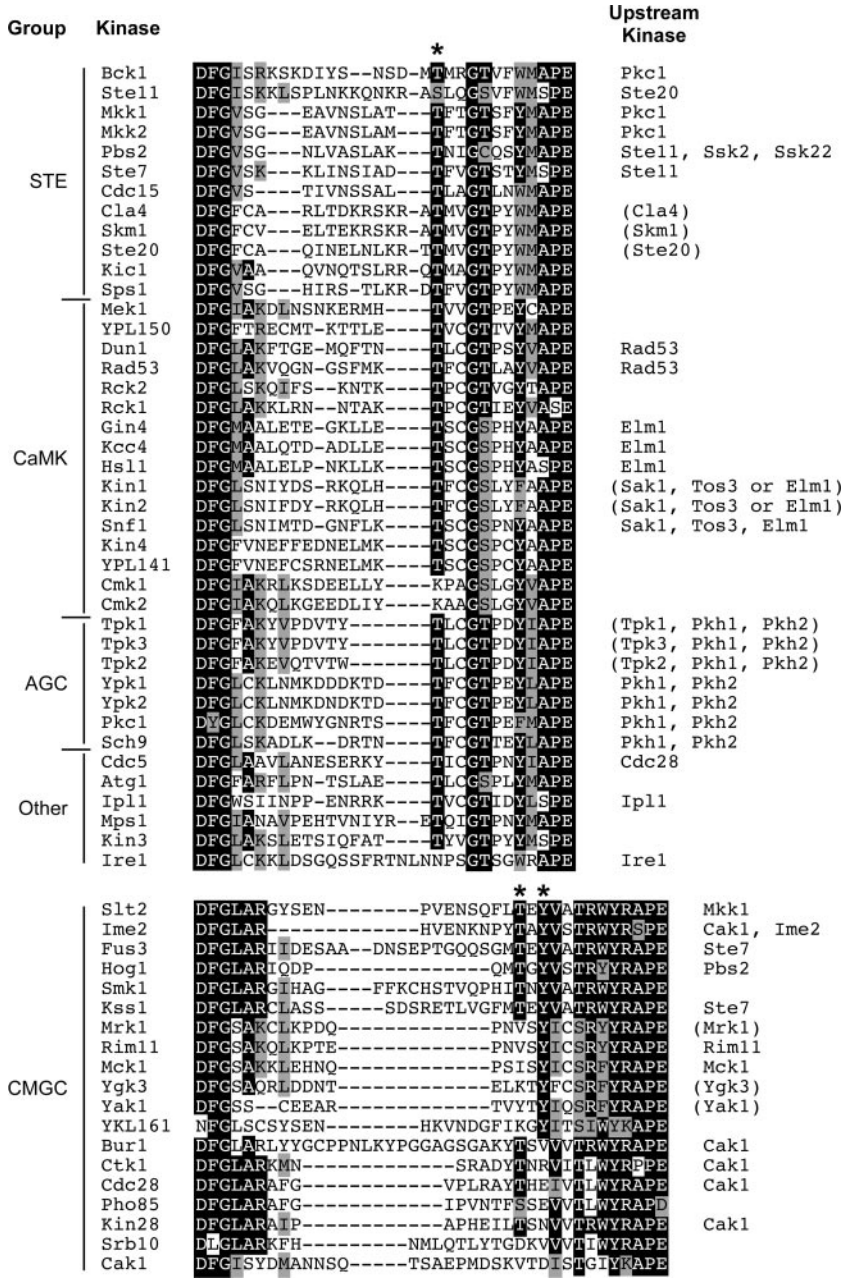

FIG. 2. Multiple sequence alignments of kinase activation loops. Activation loops were selected to highlight the presence or absence of the conserved phosphorylation sites (indicated by asterisks). The upstream kinase(s) that phosphorylates the activation loop is shown on the right. Upstream kinases predicted from results for other species or from paralogues are shown within parentheses.

target sites in their loops (Fig. 2) even though orthologues from other species contain the conserved sites and are known to be activated by upstream kinases (196). Of the six MAPKs in yeast, one, YKL161C, is uncharacterized and is the only MAPK in yeast to lack the conserved threonine in its activation loop. Most MAPKs are phosphorylated at two nearby sites in the activation loop sequence TXY. YKL161C has the sequence KGY at this position, suggesting that its regulation is likely to be different from those of the other MAPKs. Likewise, Srb10 is a CDK that lacks the conserved threonine that is present in the activation loops of the other CDKs, suggesting that Srb10 may not be regulated by activation loop phosphorylation. Experiments with Srb10 and a temperature-sensitive Cak1 support this idea (50). However, sequence analysis alone is not always sufficient for accurate prediction. Pho85, another CDK, contains potential phosphorylation sites; yet, they are not required for activation (147). Conversely, Bud32 lacks the conserved phosphorylation sites in its unusually small activation loop and yet it is activated by activation loop autophosphorylation (53).

While tyrosine phosphorylation is relatively rare in *S. cerevisiae*, one site where it does occur more frequently is in the

activation loops of kinases in the CMGC group (Fig. 2). The MAPKs are typically phosphorylated on both threonine and tyrosine residues in the TXY motif. This reaction is carried out by their respective MAPK kinases, which are capable of phosphorylating both residues (23, 47, 127). Kinases in the dual-specificity tyrosine phosphorylation-regulated protein kinase (DYRK) and GSK families are autophosphorylated on a single tyrosine residue in their activation loops. Mck1 and Rim11, two of the four yeast GSKs, have been shown to autophosphorylate on activation loop tyrosine residues (109, 247). Recent work with metazoan DYRKs and GSKs has illuminated the mechanism by which serine/threonine kinases can autophosphorylate tyrosine residues. These protein kinases are maintained during translation in an intermediate, metastable conformation by protein chaperones. In this state, they autophosphorylate their activation loop tyrosine residues in *cis*. Following the completion of translation and tyrosine autophosphorylation, these kinases adopt their mature and more stable conformation such that their substrate specificities become restricted to serine and threonine residues (113, 114). These studies predict that the two remaining yeast GSKs, Mrk1 and Ygk3, as well as the yeast DYRK, Yak1, will be similarly regulated.

Phosphorylation outside the activation loop. Many kinases are regulated by phosphorylation at sites outside their activation loops. In contrast to activation loop phosphorylation, which is always activating, phosphorylation outside the activation loop can either stimulate or inhibit a kinase. The morphogenetic checkpoint illustrates two salient examples of this type of regulation. The Swe1 kinase phosphorylates Tyr19 of Cdc28, inactivating the kinase activity of Cdc28 needed for cell cycle progression. Swe1-mediated phosphorylation declines when Swe1 protein at the bud neck is itself phosphorylated by Cdc5 and Cla4 (186) as well as by Cdc28 (6, 72, 131), leading to its ubiquitination and subsequent proteolysis. This one regulatory pathway shows two examples of inactivating phosphorylation events, one causing reduced kinase catalytic activity and the other leading to degradation. Examples of activating phosphorylation events outside the loop include those that promote binding of other proteins (12) or counter autoinhibition (17).

Dephosphorylation. For those studying the regulation of protein kinases, it is not difficult to develop (even unwittingly) a kinase-centric worldview, whereby the phosphorylation events regulating pathways and enzymes are analyzed in terms of phosphate addition alone. In reality, the phosphorylation statuses of most substrates are a reflection of the equilibrium of phosphate addition by a kinase and phosphate removal by a phosphatase. At the moment, kinases are better studied than are phosphatases. Indeed, in analysis of phosphorylation sites, the responsible kinase has been identified in many more cases than has the phosphatase. Nonetheless, the dephosphorylation of protein kinases has regulatory consequences and can be either activating or inactivating. The CDK Cdc28 is an excellent example of both forms of regulation. Cdc28 activation requires both the phosphorylation of its activation loop by Cak1 (89) and the dephosphorylation of the Tyr19 site in its N terminus by the dual-specificity phosphatase Mih1 (184).

Protein binding. Protein-protein interaction is another major regulatory motif controlling the activities of protein kinases. Members of each major group of protein kinases are regulated by interaction of the kinase domain with other protein domains in either *cis* or *trans*. Association with protein binding partners can modulate the activation states of kinases in multiple ways. Elegant structural studies have elucidated the manner by which protein binding dictates the activities of several kinases.

Crystallographic studies have illuminated the mechanism by which the mammalian p21-activated kinases (PAKs) are activated by physical association with GTP-bound p21 proteins (106, 158). Binding of p21 shifts a mammalian PAK from a homodimeric autoinhibited conformation to an active form capable of *trans*-autophosphorylation. In *Saccharomyces cerevisiae*, three sterile (STE) group constituents are PAK family members: Cla4, Skm1, and Ste20. Two of the three, Cla4 and Ste20, have been shown to be activated by association with p21 family member Cdc42. Skm1 contains a highly homologous N-terminal autoinhibitory domain and is predicted to be similarly activated. Based on the regulation of their metazoan orthologues, we predict that binding of Cdc42 to the yeast PAKs promotes *trans*-autophosphorylation of the conserved threonine residues in their activation loops (Fig. 2). Another example of a kinase being activated by the binding of a small GTP-binding protein is Pkc1. Binding of the GTP-bound form of Rho1 to Pkc1 enables Pkc1 to respond to activating cofactors (91). This regulatory mechanism makes the yeast Pkc1 similar to the mammalian PRK2 kinase, which is activated by Rho binding (222).

Another well-characterized example of regulation by physical association with protein binding partners is the activation of CDKs by their cognate cyclins. Again, X-ray crystal structures with a mammalian CDK and cyclin pair serve as a paradigm for understanding the mechanism by which physical association of cyclin with CDK results in kinase activation (85). Cyclin binding induces the proper alignment of active site residues such that they are catalysis competent. Additionally, the activation loop, once crisscrossing and occluding the active site, shifts position upon association with cyclin, relieving steric hindrance to ATP entry as well as becoming available for phosphorylation by a CDK-activating kinase. Yeast encodes multiple CDKs (Cdc28, Pho85, Srb10, Kin28, and Bur1) that are activated by interaction with one or multiple cyclin partners. Additionally, Ctk1 activation requires interaction with the cyclin-related protein Ctk2 (73, 203).

In addition to activating interactions, some protein-protein interactions lead to inhibition of kinase activity. Some kinases, Rck2 and Snf1 for example, contain autoinhibitory domains within the kinase polypeptide but outside the kinase domain. Though the molecular mechanism of the inhibition is not yet known, the inhibitory effects of these domains can be overcome by phosphorylation in the case of Rck2 (17) or additional protein-protein interactions in the case of Snf1 (86). In the case of the cyclic AMP-dependent protein kinase, the association of the regulatory subunit places a pseudosubstrate peptide in the active site of the catalytic subunit, thereby blocking substrate access (40, 204). Whether other inhibitory interactions also involve a pseudosubstrate mechanism remains to be determined.

Binding nonprotein ligands. While many kinases are controlled by their interactions with other proteins or protein domains, a few are regulated by binding nonprotein ligands. In

all documented cases in yeast, these interactions stimulate the activities of the respective kinases. Though the biochemical mechanism is not yet clear, the sphingoid long-chain base phytosphingosine activates kinase Pkh1 of the AGC group (a kinase family that includes protein kinase A [PKA], PKG, and PKC) (112). Cyclic AMP binding of the PKA regulatory subunit Bcy1 results in its dissociation from and subsequent activation of redundant catalytic subunits Tpk1, Tpk2, and Tpk3 (87). The related proteins Cmk1 and Cmk2 are both activated by interaction with calmodulin protein complexed with four calcium ions (152, 159). In addition to interaction with Cdc42 (discussed above), Cla4 requires association with the plasma membrane lipid phosphatidylinositol 4-phosphate (PI4P) via its pleckstrin homology domain for its role in regulating cellular morphogenesis and the mitotic exit network (233). The protein kinase Gcn2 senses and is activated by amino acid starvation by virtue of binding uncharged tRNA molecules (171). In addition, the PAS domain kinases (PASKs), Psk1 and Psk2, as well as Snf1 may someday be added to the list of kinases regulated by ligands since these kinases (or associated subunits) have domains that are known to bind ligands in other systems (34, 195).

Accumulation. Kinases are also regulated by management of protein accumulation. Hsp90 and its cochaperone Cdc37 play an important role in the folding and accumulating of many if not most yeast protein kinases (121). The interaction of kinases with chaperones may also regulate kinase activity by controlling the transition between active and inactive conformations (1, 42, 63). The abundance of specific kinases may be modulated by changes in expression at the level of mRNA, protein, or both. We have made no attempt to review or assess the volumes of microarray data. Here, we have limited our review to kinases whose abundance has been studied individually. For instance, Smk1 is required for spore morphogenesis, and its mRNA expression is induced during sporulation (163). Ste7 (226) and Swe1 (25), by contrast, are regulated at the level of protein stability via the ubiquitin degradation pathway.

Localization. The final paradigm of kinase regulation is subcellular localization. Like protein accumulation, this mechanism does not necessarily involve a change in intrinsic catalytic activity but serves to position the enzyme at the right place and time to perform its respective function. The protein kinase Elm1 is localized to the bud neck in its role in regulating the morphogenetic checkpoint; mutations that misdirect the subcellular localization of Elm1 prevent Elm1 from phosphorylating critical substrates, resulting in aberrantly elongated morphology (21). In another example of regulated subcellular localization, PKA-dependent phosphorylation of Rim15 (outside its activation loop) tethers Rim15 in the cytoplasm by promoting association with 14-3-3 proteins Bmh1 and Bmh2. Upon dephosphorylation, Rim15 dissociates from the 14-3-3s and translocates to the nucleus, whence it initiates the G_0 program (229). Many more examples of kinases that are regulated by their localization will no doubt be uncovered in the future.

CONCLUSIONS

Organizing the protein kinases of *Saccharomyces cerevisiae* by regulatory mechanisms provides a useful genome-wide perspective on how these enzymes are controlled. While some regulatory motifs are represented more heavily in particular groups and families, there is an otherwise broad distribution of mechanisms across the phylogenetic spectrum. This review highlights the wealth of research that has been conducted to understand how protein kinases are regulated. It also makes clear that there is still much work to be done. Currently, no regulatory mechanism has been reported for 36 yeast kinases. However, for several of these uncharacterized enzymes, we have used the regulation of related kinases to predict plausible modes for their regulation. We hope that this review will help investigators as they design experiments to test these and other predictions based on the regulation of related kinases.

ACKNOWLEDGMENTS

We are indebted to Gerard Manning for current kinase classification and Pekka Lappalainen for explaining the misannotation of twinfilin. We thank Jeremy Thorner, Ed Winter, and our anonymous reviewers for helpful comments.

This work was supported by grant GM46443 from the National Institutes of Health (to M.S.) and American Heart Association predoctoral fellowship 0615379U (to E.R.).

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