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Letter to the Editor

A Unified Nomenclature for Protein Subunits of Mediator Complexes Linking Transcriptional Regulators to RNA Polymerase II

Promoter-specific initiation of transcription by RNA polymerase II (Pol II) requires both gene-specific regulators and general transcription factors (GTFs: TFIIB, -D, -E, -F, and -H) (Woychik and Hampsey, 2002). Biochemical and genetic studies in yeast led to the discovery of a Mediator (MED) complex of 20 protein subunits, linking transcriptional regulators to Pol II and GTFs (Flanagan et al., 1991; Kelleher et al., 1990; Kim et al., 1994). In vitro, Mediator stimulates basal transcription, enables activated transcription, and relieves the interfering effect (Gill and Ptashne, 1988) of a strong transcriptional activator (Kim et al., 1994). The identification of Mediator subunits revealed that many were products of previous genetic screens (Carlson, 1997; Lee and Young, 2000; Myers and Kornberg, 2000; Nonet and Young, 1989; Suzuki et al., 1988), and some were shown to interact directly with Pol II and GTFs (Koleske et al., 1992; Myers et al., 1998; Sakurai and Fukasawa, 2000; Thompson et al., 1993). Further genetic studies demonstrated the role of Mediator in repression as well as activation (Li et al., 1995; Song et al., 1996), and established the relevance of Mediator to transcription control in vivo (Barberis et al., 1995; Holstege et al., 1998; Thompson and Young, 1995).

For some time there was no evidence for conservation of yeast Mediator through evolution. However, independent biochemical and structural studies of coactivators that, in most cases, were initially identified in functional assays have revealed true counterparts in other fungi and in higher organisms (Asturias et al., 1999; Boyer et al., 1999; Chao et al., 1996; Fondell et al., 1996; Gu et al., 1999, 2002; Ito et al., 1999; Jiang et al., 1998; Kretzschmar et al., 1994; Kwon et al., 1999; Malik et al., 2000; Meisterernst et al., 1991; Naar et al., 1999; Park et al., 2001; Rachez et al., 1999; Ryu et al., 1999; Spahr et al., 2001; Sun et al., 1998). In mammals, the positive cofactor (PC2) component of the USA coactivator activity (Kretzschmar et al., 1994; Meisterernst et al., 1991) proved to be a Mediator-related complex (Malik et al., 2000). Similarly, the human TRAP complex, first identified as a discrete group of thyroid hormone receptor-associated polypeptides with a potent coactivator activity (Fondell et al., 1996), also was found to represent a Mediator equivalent (Ito et al., 1999). Other metazoan Mediator-related complexes have been denoted ARC, CRSP, or DRIP owing to interactions with other nuclear receptors as well as diverse transcriptional activators (Mittler et al., 2003; Naar et al., 1999; Rachez et al., 1999; Ryu et al., 1999; Yang et al., 2004).

A systematic analysis of proteins present in the most highly purified mammalian complexes by tandem mass spectrometry led to the identification of up to 30 distinct MED subunits (MEDs) (Sato et al., 2003a; Tomomori-Sato et al., 2004). Initial studies identified 8 MEDs conserved from fungi to humans: Med6/Pmc5/ARC/DRIP33/TRAP32, Med7/ARC/DRIP/TRAP34/CRSP33, Nut2/Med10/TRAP15, Srb7/SURB7/TRAP19, Rgr1/Pmc1/ARC/CRSP/DRIP150/TRAP170, Soh1/TRAP18 (note that Soh1 has not been yet identified in purified yeast Mediator), Srb10/Ssn3/Ume5/Gig2/Nut7/Rye5/CDK8, and Srb11/Ssn8/Ume3/Gig3/Nut9/Rye2/Cyclin C) (for reviews see Malik and Roeder, 2000; Rachez and Freedman, 2001). However, extensive cross-species comparisons in several labs have more recently detected metazoan counterparts for nearly all yeast MEDs (see Table 1) (Borggrefe et al., 2002; Boube et al., 2002; Gustafsson and Samuelsson, 2001; Samuelsen et al., 2003; Sato et al., 2003b; Spahr et al., 2001; Tomomori-Sato et al., 2004). Further bioinformatics analyses and functional studies have revealed that the human MEDs ARC105 and yeast Gal11 harbor an activator-targeted domain related to the KIX domain found in the CBP/p300 coactivators, suggesting that ARC105 and Gal11 are evolutionarily related (Novatchkova and Eisenhaber, 2004; A.M.N., unpublished data). The time now seems right to establish a unified MED nomenclature in order to enhance understanding of the scientific literature by a wide audience and to aid cross-species comparisons and proper annotation of sequence databases.

The unified nomenclature, shown in Table 1, is based on the following considerations:

1. The new nomenclature complies with guidelines endorsed by the *Saccharomyces* Genome Database (SGD), the FlyBase and WormBase resources, and the human HUGO Gene Nomenclature Committees.
2. MED is the most explicit acronym.
3. This nomenclature acknowledges the discovery of MED complexes in yeast.
4. In light of point 3, the original yeast MEDs will retain their names (MED1-11; note that the MED5 acronym will replace Nut1).
5. The remaining yeast MEDs will be given names starting from MED12, in order of decreasing conceptual molecular weights deduced from primary sequences.
6. MEDs found outside budding yeast will be given names starting from MED23 in order of decreasing calculated molecular weights (based on the human protein). At present, this list extends to MED31.
7. Future bona fide new MED components will be assigned numbers starting from MED32.
8. The general nomenclature will employ CDK8 and CycC, as the CDK-cyclin couple is readily identifiable for a wide scientific audience.
9. Except for the specific case of *C. elegans* (see point 10), paralogs in the same organism will be termed MED-like, e.g., MED12L in humans.
10. *C. elegans* MEDs will retain the specific nomenclature already adopted by WormBase, the MED acronym being used for another gene category. Thus

Table 1. New Nomenclature for MED Subunits Including the Corresponding Known or Predicted Orthologs and Paralogs

New name	*S. cerevisiae*[a]	*S. pombe*	*C. elegans*		*D. melanogaster*[c]	*H. sapiens*[d]				
			Previous name[b]	New name		TRAP/SMCC	ARC/DRIP	CRSP	PC2	OTHERS
MED1	Med1	Pmc2	SOP-3*	MDT-1.1	Trap220*	TRAP220	ARC/DRIP205	CRSP200	TRAP220	PBP
MED1L			T23C6.1*	MDT-1.2						
MED2	Med2									
MED3	Pgd1/Hrs1/Med3									
MED4	Med4	Pmc4/SpMed4	ZK546.13*	MDT-4	Trap36	TRAP36	ARC/DRIP36		TRAP36	p34
MED5	Nut1									
MED6	Med6	Pmc5/SpMed6	LET-425/MED-6	MDT-6	Med6	hMed6	ARC/DRIP33		hMed6	p32
MED7	Med7	SpMed7	LET-49/MED-7	MDT-7	Med7*	hMed7	ARC/DRIP34	CRSP33	hMed7	p36
MED8	Med8	Sep15/SpMed8	Y62F5A.1b*	MDT-8	Arc32*		ARC32			mMed8
MED9	Cse2/Med9				CG5134*					Med25
MED10	Nut2/Med10	SpNut2	T09A5.6	MDT-10	Nut2*	hNut2	hMed10		hNut2	
MED11	Med11		R144.9*	MDT-11	Med21					HSPC296
MED12	Srb8	SpSrb8	DPY-22/SOP-1*	MDT-12	Kto*	TRAP230	ARC/DRIP240			
MED12L										TRALPUSH*
MED13	Ssn2/Srb9	SpTrap240	LET-19*	MDT-13	Skd/Pap/Bli*	TRAP240	ARC/DRIP250			
MED13L										PROSIT240
MED14	Rgr1	Pmc1/SpRgr1	RGR-1*	MDT-14	Trap170	TRAP170	ARC/DRIP150	CRSP150	TRAP170	p110
MED15	Gal11	SpGal11*	R12B2.5b*	MDT-15	Arc105*		ARC105		PCQAP	TIG-1
MED16	Sin4				Trap95*	TRAP95	DRIP92		TRAP95	p96b
MED17	Srb4	SpSrb4	Y113G7B.18*	MDT-17	Trap80	TRAP80	ARC/DRIP77	CRSP77	TRAP80	p78
MED18	Srb5	Pmc6/Sep11	C55B7.9*	MDT-18	p28/CG14802					p28b
MED19	Rox3	SpRox3	Y71H2B.6*	MDT-19	CG5546*					LCMR1
MED20	Srb2	SPAC17G8.05*	Y104H12D.1*	MDT-20	Trfp	hTRFP			hTRFP	p28a
MED21	Srb7	SpSrb7	C24H11.9*	MDT-21	Trap19	hSrb7	hSrb7		hSrb7	p21
MED22	Srb6	SpSrb6	ZK970.3*	MDT-22	Med24					Surf5
MED23			SUR-2*	MDT-23	Trap150β*	TRAP150β	ARC/DRIP130	CRSP130	TRAP150β	hSur2
MED24					Trap100*	TRAP100	ARC/DRIP100	CRSP100	TRAP100	
MED25					Arc92*		ARC92			ACID1
MED26					Arc70*		ARC70	CRSP70		
MED27		Pmc3	T18H9.6*	MDT-27	Trap37*	TRAP37		CRSP34	TRAP37	
MED28			W01A8.1*	MDT-28	Med23					Fksg20
MED29			K08E3.8*	MDT-29	Intersex*					Hintersex
MED30					Trap25	TRAP25				
MED31	Soh1*	SpSoh1/Sep10*	F32H2.2*	MDT-31	Trap18	hSoh1			hSoh1	
CDK8	Srb10/Ssn3/Ume5	SpSrb10	CDK-8*		Cdk8	hSrb10	CDK8			
CycC	Srb11/Ssn8/Ume3	SpSrb11	H14E04.5*	CIC-1	CycC	hSrb11	CycC			

[a]From SGD.
[b]From WormBase.
[c]From FlyBase.
[d]Acronyms given to MEDs identified from various mammalian MED-like complexes (Malik and Roeder, 2000). Many of the components listed under Others recently have been found in both the larger and smaller complexes; however, the MED12, MED13, CDK8, and CycC components clearly are not present in the smaller complexes, consistent with their absence in a subpopulation of yeast Mediator complexes.
Asterisks indicate that the corresponding proteins have not yet been identified in purified MED complexes.

MDT-6 (for Mediator-6) replaces MED6, but the proposed numbering from 1 to 31 would be retained. In addition, following usual recommendations in this organism, the two MED1 paralogs would be called MDT-1.1 and MDT-1.2.

We believe the relative simplicity of the new, common nomenclature will expedite functional comparisons in different species, while remaining flexible enough to accommodate additional species-specific MEDs as they arise. Some uncertainties persist concerning the assignments of orthologous subunits, and the nomenclature can be updated if new data so require. To facilitate communication between researchers working inside and outside of the transcription field, we recommend that this numbering system be used in all future publications concerning Mediator complexes.

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