

Dual-specificity phosphatases in

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igur	e larget	lissue/Cell line	Cat#
Α.	DUSP4	Human breast carcinoma	AP8447b
В.	CDC25B	Human breast carcinoma	AP7256c
C.	CDK1	Human breast carcinoma	AP7517d
D.	CDK6	Human breast carcinoma	AP7522b
Ε.	PDGFRA	Human carcinoma (HeLa)	AP7666j
F.	DUSP6	Human carcinoma (HeLa)	AT1830a
G.	Cyclin D1	Mouse lung tissue lysate	AP2612d
Н.	Cyclin E1	A2058 cell line lysate	AP6270b
Ι.	CDC25A	HeLa cell line lysate	AP6272c
J.	CDK2	Jurkat cell line lysate	AP7518b
К.	CDK4	HL-60 cell line lysate	AP7520b
L.	Cyclin B1	NCI-H460 cell line lysate	AP7598a
М.	DUSP3	SK-BR-3 cell line lysate	AP8478a



Dual-specificity phosphatases



Fig. 1 CDC25 phosphatases promote mammalian cell-cycle progression. Dualspecificity phosphatases (DSPases) have a central role in the complex regulation of signaling pathways that are involved in cell stress responses, proliferation and death (1). The cell-division cycle 25 (CDC25) family of DSPases regulates cell-cycle progression by dephosphorylating and activating cyclin-dependent kinases (CDKs). In the event of DNA damage, CDC25 are key targets of the checkpoint machinery that ensures genetic stability. Inactive CDKs are phosphorylated at adjacent threonine and tyrosine residues near their amino termini. Dephosphorylation at both sites by CDC25 phosphatases catalyses their activation and allows the CDKs to propagate cell-cycle signal transduction (1-12). Indicated in red are the protein targets for ABGENT's antibody products.

Examples for dual-specificity phosphatases and their biological functions

Gene	Name	Role in nuclear signaling	Cellular process / disease	
CDC25A, B, C	cell-division cycle 25	DNA damage	Cell cycle control, checkpoint pathways	
CDC14A, B, C	cell division cycle 14	p53 regulation	Cell cycle control, cytokinesis, cancer	
PTEN	phosphatase and tensin homolog	DNA repair	Cell cycle control, chromosome stability	
PTPN11	SHP2	Transcriptional regulation	Mitogenic activation, metabolic control	
DUSP1	dual-specificity phosphatase 1	Transcriptional regulation	Cell cycle control, immune response	
DUSP2	dual-specificity phosphatase 2	Nuclear accumulation of ERK	Immune response, heat shock	
DUSP4	dual-specificity phosphatase 4	Nuclear accumulation of ERK	Control of cell cycle and MAP kinases	
DUSP5	dual-specificity phosphatase 5	Nuclear translocation	Immune response	
DUSP6	dual-specificity phosphatase 6	FGF signaling to the nucleus	Development, postnatal lethality	
DUSP7	dual-specificity phosphatase 7	FGF signaling to the nucleus	Development	
DUSP9	dual-specificity phosphatase 9	Transcriptional regulation	Development	
DUSP10	dual-specificity phosphatase 10	Transcriptional regulation	Immune response	
DUSP12	dual-specificity phosphatase 12	Heat stress response	Cell survival, diabetes	
DUSP14	dual-specificity phosphatase 14	Transcriptional regulation	Immune response, CD28 signaling	
DUSP22	dual-specificity phosphatase 22	STAT3 activation, ER $lpha$ signaling	Immune response, proliferation	
EPM2A	laforin	β -catenin accumulation in nucleus	Lafora progressive myoclonus epilepsy	

Overexpression of CDC25 in cancer Thyroid 17-69% N 36-64% Y Gliomas Thyroid 17-69% N 26-64% Y Laryngeal









Fig. 2 Overexpression of CDC25 protein in human cancers. CDC25 proteins are overexpressed in a wide variety of cancers. Percentages of tumors in which CDC25A, CDC25B or CDC25C are overexpressed are indicated. CDC25 overexpression is linked to clinicopathological features, including tumor grade or stage, metastases, depth of invasion, residual or recurrent disease. Cases for which several studies reported contradictory prognostic values are marked by a (C), and studies in which clinicopathological features were not assessed are indicated by an (?). The intensity of the red circles in the human body corresponds to the cancer mortality (2, 5).

Fig. 3 Domain organization of CDC25 homologs (A) and detection of CDC25 in transfected cells (B, C). ABGENT's antibody #AP3048a was generated against synthetic phosphopeptide corresponding to amino acids surrounding S292 of human CDC25A (B). The antibody was used in Western blot to detect Phospho-CDC25A-S292 in cells transfected with wild type (wt) or mutant S292A of CDC25A. Antibody #AP3051 a was generated against phosphopeptide corresponding to amino acids surrounding T506 of human CDC25A (C). The antibody was used to detect Phospho-CDC25A-T506 in cells transfected with wild type or mutant T506A of CDC25A.

Product abbreviations

DUSP4: dual specificity phosphatase 4; MAP kinase phosphatase 2; VH1 homologous phosphatase 2 CDC25A & B: cell division cycle 25 homolog A & B CDK1: cell division cycle 2, G1 to S and G2 to M; cyclin-dependent kinase 1; p34 protein kinase; CDC2 CDK6: cyclin-dependent kinase 6; cell division protein kinase 6 PDGFRA: platelet-derived growth factor receptor, alpha polypeptide DUSP6: dual specificity phosphatase 6; MAP kinase phosphatase 3 Cyclin D1: B-cell CLL/lymphoma 1; G1/S-specific cyclin D1; CCND1 Cyclin E1: cyclin Es; cyclin Et; CCNE1 CDK2: cyclin-dependent kinase 2; cdc2-related protein kinase; cell devision kinase 2; p33 protein kinase CDK4: cyclin-dependent kinase 4; cell division kinase 4; melanoma cutaneous malignant, 3 CCNB1: G2/mitotic-specific cyclin B1; CCNB1 DUSP3: dual specificity phosphatase 3; vaccinia virus phosphatase VH1-related; VHR

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Fig.4 Control of the cell cycle by the ubiquitin-proteasome system. The cell division cycle is regulated primarily by the activity of cyclindependent kinases (CDKs) and protein degradation by the ubiquitin-proteasome system (UPS). Each CDK complex contains one of many activating subunits, termed cyclins, the levels of which oscillate during the cell cycle. CKIs (CDK inhibitors), such as p27 and p21, inhibit CDK activity and promote cell cycle arrest and/or delay. SCF complexes and the APC/C (anaphase-promoting complex/cyclosome) provide the specific, rapid and timely proteolysis of cell cycle regulators, which ultimately controls CDK1 and CDK2 to finely modulate their activities during cell cycle progression. The best characterized cell cycle ubiquitin ligases are SCFSKP2, SCFFBXW7 (not shown), SCF β -TrCP, APC/CCD11 and APC/CCDC20. SCFSKP2 is a positive regulator of the cell cycle (by targeting CDC25A (cell division cycle 25A), claspin, WEE1 and EMI1 (also known as F-box protein 5)). APC/CCD11 and APC/CCDC20 always attenuate CDK1 activity (by directing the degradation of cyclins A and B), except in early mitosis, when APC/CCDC20 targets p21 for degradation. Finally, SCFFBXW7 attenuates CDK1 and CDK2 by inducing the degradation of cyclin E. SCF complexes and the APC/C control each other, with SKP2 being ubiquitylated by APC/CCD11 in G1 and SCF β -TrCP targeting EMI1, which is an inhibitor of APC/CCDC11, for proteolysis in early mitosis. Additionally, SCF complexes and the APC/C share common substrates that are targeted by their respective ubiquitin ligase(s) only at particular times during the cell cycle. For example, SCFSKP2 targets p21 for degradation of CDC25A by APC/CCDC11 in G1 phase, which is followed by SCF β -TrCP-mediated degradation during S phase. Moreover, phosphorylation by CDKs modulates the activity of SCF complexes and the APC/C. CDK activity inhibits binding of CDH1 to the APC/C while promoting the activation of APC/CCDC20, and phosphorylation of certain SCF substrates by CDKs allows recog

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