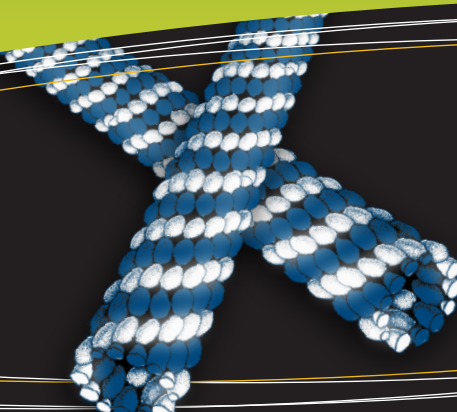




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this issue

HDAC6 interaction with tubulin HSP90 and Cortactin

Tubulin Publications

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HDAC6: An update on its interaction with tubulin, HSP90 and Cortactin

Since the discovery that HDAC6 deacetylates Lys40Ac of alpha-tubulin (1,2), researchers have explored its functions in health and disease. Three main molecular functions have emerged for this enzyme: 1. Deacetylating tubulin, destabilizing microtubules and making them more dynamic (2), 2. Regulating denatured protein aggregation prior to degradation (3,4,5), and 3. Deacetylating cortactin (6) which mediates cell movement and blood vessel formation (6,7).

HDAC family members were re-classified by Ruijter et al. (8) to incorporate original HDAC members and the new class of NAD-dependent HDACs called Sirtuins (Sir2). The eighteen members were classified into Classes I through IV based on their homology to the four yeast HDAC genes. Classes I and II relate to yeast homologs RPD3 and HDA1, respectively, and contain the original HDACs, whereas III and IV relate to the Sirtuins. Class I HDACs reside predominantly in the nucleus, whereas Class II can be found in the nucleus or cytoplasm. HDAC6 is placed into Class II and has three unique features which relate to its function. First, it contains a nuclear exclusion sequence which encodes its preference for the cytoplasm over the nucleus. Second, it has a ubiquitin binding domain, thus identifying it as a member of the protein degradation pathway. Third, it has two deacetylase domains which modify its substrates: tubulin, HSP90 and cortactin.

The molecular functions of HDAC6 manifest themselves in different ways depending on the cellular background.

For example, in fibroblasts HDAC6 regulates microtubule dynamics, which in turn regulates the rate of turnover of focal adhesions and affects cell migration (9). However, in more static cells like retinal epithelial and neuronal cells, the main function is to regulate the formation of aggresomes using microtubules as tracks to the processing site (3,4,5) (Figure 1). As a third example, in vascular epithelial cells (6,7) HDAC6 is upregulated under hypoxic conditions and is essential for angiogenesis. Subsequently, researchers found that cortactin was a substrate of HDAC6 and that its deacetylation regulates epithelial cell migration and hence vessel formation. A similar situation involves osteoclast maturation where HDAC6 regulates podosome formation (10).

Researchers have utilized several tools to investigate the functions of HDAC6, these including knock-out mice, siRNA, mutant HDAC6 proteins and small molecule inhibitors. Three inhibitors used to study HDAC6 activity in the context of other HDACs are Tubacin, Tubastatin A and Trichostatin A. Trichostatin A was the original HDAC inhibitor identified by Yoshida et al. (11). It was later shown to be a potent inhibitor of Class I & II HDACs (14). Tubacin was developed by Haggarty et al. (10) as a domain selective inhibitor for the tubulin HDAC domain in HDAC6. Tubacin has now been superseded by a more HDAC6 selective compound called Tubastatin A (13).

For more information about HDAC6, tubulin and aggresomes, see these reviews (14, 15).

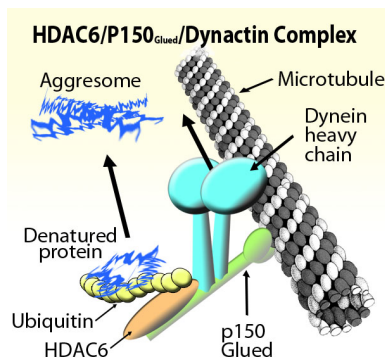


Figure 1. The dynactin-p150Glued complex is thought to bind HDAC6 during its role as an HSP90 transport regulator, the complex follows the microtubule track to deposit the denatured protein in the aggresome prior to its proteolytic degradation.

Upcoming Meetings

- Neuroscience Nov 12-16
- AACR-NCI-EORTC Nov 12-16
- ASCB Dec 3-7

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References & Reviews

- Matsuyama A, Shimazu T, et al. 2002. In vivo destabilization of dynamic microtubules by HDAC6-mediated deacetylation. *EMBO J.* 21(24),6820-6831.
- Hubbert C, Guardiola A, Shao R, Kawaguchi Y, Ito A, Nixon A, Yoshida M, Wang X-F, and Yao T-P. 2002. HDAC6 is a microtubule-associated deacetylase. *Nature*, 417, 455-458.
- Pandey UB, Nie Z, et al. 2007. HDAC6 rescues neurodegeneration and provides an essential link between autophagy and the UPS. *Nature*, 447(7146), 859-863.
- Lee JY, Koga H, et al. 2010. HDAC6 controls autophagosome maturation essential for ubiquitin-selective quality-control autophagy. *Embo J.* 29(5), 969-980.
- Ryhanen T, Viiri J, Hyttinen JMT, Uusitalo H, Salminen A, and Kaamiranta K. 2010. Influence of Hsp90 and HDAC inhibition and Tubulin acetylation on perinuclear protein aggregation in human retinal pigment epithelial cells. *J. Biomed. Biotechnol.*, doi:10.1155/2011/798052.
- Zhang X, Yuan Z, et al. 2007. HDAC6 modulates cell motility by altering the acetylation level of cortactin. *Mol. Cell*, 27(20), 197-213.
- Kaluza D, Kroll J. et al. 2011. Class IIb HDAC6 regulates endothelial cell migration and angiogenesis by deacetylation of cortactin. *Embo J.*, doi:10.1038/emboj.2011.298 .
- de Ruijter AJM, van Gennip AH, Caron HN, Kemp S, and van Kuilenburg ABP. 2003. Histone deacetylases (HDACs): characterization of the classical HDAC family. *Biochem. J.* 370, 737-749.
- Tran A D-A, Marmo TP, et al. 2007. HDAC6 deacetylation of tubulin modulates dynamics of cellular adhesions. *J. Cell Sci.*, 120, 1469-1479.
- Destaing O, Saltel F, Gilquin B, Chabadel A, Khochbin S, Ory S. and Jurdic P. 2005. A novel Rho-mDia2-HDAC6 pathway controls podosome patterning through microtubule acetylation in osteoclasts. *J. Cell Sci.*, 118, 2901-2911.
- Yoshida M, Kijima M, Akita M, Beppu T. 1990. Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A. *J Biol Chem.* 265(28), 17174-9.
- Haggarty SJ, Koeller KM, Wong JC, Grozinger CM, and Schreiber S. 2003. Domain selective small-molecule inhibitor of histone deacetylase 6 (HDAC6)-mediated tubulin deacetylation. *Proc. Natl. Acad. Sci. USA*, 100 (8), 4389-4394. doi/10.1073/pnas0430973100.
- Butler KV, Kalin J, Brochier C, et al. 2010. Rational design and simple chemistry yield a superior, neuroprotective HDAC6 inhibitor, Tubastatin A. *J Am Chem Soc*, 132(31), 10842-6.
- Valenzuela-Fernandez A, Cabrero JR, Serrador JM and Sanchez-Madrid F. 2008. HDAC6: a key regulator of cytoskeleton, cell migration and cell-cell interactions. *Trends Cell Biol.* 18, p.291-297.
- Li G, Jiang H, Chang M, Xie H and Linsen Hu. 2011. HDAC6 α -tubulin deacetylase: A potent therapeutic target in neurodegenerative diseases. *J. Neurol. Sci.*, 304, p.1-8.

Tubulin Tools

Proteins (Labeled, Unlabeled, Microtubules)	Tubulin Proteins				
	Tubulin Proteins	Source	Purity	Cat. #	Amount
Tubulin Protein without glycerol	T238P-A	Porcine Brain	>99%	T238P-A	1 x 1 mg
	T238P-B T238P-C			T238P-B T238P-C	5 x 1 mg 20 x 1 mg
Tubulin Protein with glycerol	T240-A	Porcine Brain	>99%	T240-A	1 x 1 mg
	T240-B T240-C T240-DX			T240-B T240-C T240-DX	5 x 1 mg 20 x 1 mg 1 x 10 mg
Tubulin Protein, MAP rich	ML116-A	Porcine Brain	70% tubulin 30% MAPs	ML116-A	1 x 1 mg
	ML116-B ML116-C ML116-DX			ML116-B ML116-C ML116-DX	5 x 1 mg 20 x 1 mg 1 x 10 mg
Tubulin for HTS Applications	HTS03-A	Porcine Brain	97%	HTS03-A	1 x 4 mg
	HTS03-B HTS03-XL			HTS03-B HTS03-XL	1 x 40 mg 1 x 100 mg
Tubulin Protein (Soybean)	<i>Glycine max</i>		>90%	TP005	1 x 250 μ g
Cancer Cell Tubulin	HeLa cells		>90%	H001-B	1 x 250 μ g
Cancer Cell Tubulin	MCF-7 cells		>90%	H005	1 x 250 μ g
Fungal Tubulin	<i>Agaricus bisporus</i>		>90%	F001	1 x 250 μ g
FtsZ Protein	Bacterial tubulin homolog		>75%	FTZ01-A	1 x 1 mg
				FTZ01-B	5 x 1 mg
AMCA Labeled Tubulin	TL440M-A	Porcine Brain	>99%	TL440M-A	5 x 20 μ g
	TL440M-B			TL440M-B	20 x 20 μ g
HiLyte Fluor™ 488 Labeled Tubulin	TL488M-A	Porcine Brain	>99%	TL488M-A	5 x 20 μ g
	TL488M-B			TL488M-B	20 x 20 μ g
TRITC Rhodamine Labeled Tubulin	TL590M-A	Porcine Brain	>99%	TL590M-A	5 x 20 μ g
	TL590M-B			TL590M-B	20 x 20 μ g
X-Rhodamine Labeled Tubulin	TL620M-A	Bovine Brain	>99%	TL620M-A	5 x 20 μ g
	TL620M-B			TL620M-B	20 x 20 μ g
HiLyte Fluor™ 647 Labeled Tubulin	TL670M-A	Porcine Brain	>99%	TL670M-A	5 x 20 μ g
	TL670M-B			TL670M-B	20 x 20 μ g
Biotin Tubulin	T333P-A	Porcine Brain	>99%	T333P-A	5 x 20 μ g
	T333P-B T333P-XL			T333P-B T333P-XL	20 x 20 μ g 1 x 500 μ g
Biotin Cancer Tubulin	HeLa cells		>90%	H003	1 x 40 μ g
Microtubules pre-formed, ready to use, lyophilized	MT002-A	Porcine brain	>99%	MT002-A	4 x 500 μ g
	MT002-XL			MT002-XL	1 x 10 mg
Microtubules pre-formed, ready to use, lyophilized	MT001-A	Bovine brain	>99%	MT001-A	4 x 500 μ g
	MT001-XL			MT001-XL	1 x 10 mg

Tubulin Kits	Tubulin Biochem Kits™	
	Cat. #	Amount
Tubulin Polymerization Assay Biochem Kit™	BK006P	24-30 assays
	>99% pure tubulin, Turbidometric-based	
Tubulin Polymerization Assay Biochem Kit™	BK004P	24-30 assays
	>97% pure tubulin, Turbidometric-based	
Tubulin Polymerization Assay Biochem Kit™	BK011P	96 assays
	>99% pure tubulin, Fluorescence-based	
Microtubule Binding Protein Spin-Down Assay Biochem Kit™	BK029	30-100 assays
	Production of fluorescent microtubules	
Fluorescent Microtubules Biochem Kit™ (rhodamine)	BK007R	50-200 assays
	Production of fluorescent microtubules	
Microtubules / Tubulin Biochem Kit™	BK015	8-200 assays
	Production of microtubules	
Microtubule / Tubulin In Vivo Assay Kit™	BK038	30-100 assays
	Quantitates <i>in vivo</i> ratio of tubulin polymers & monomers	

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