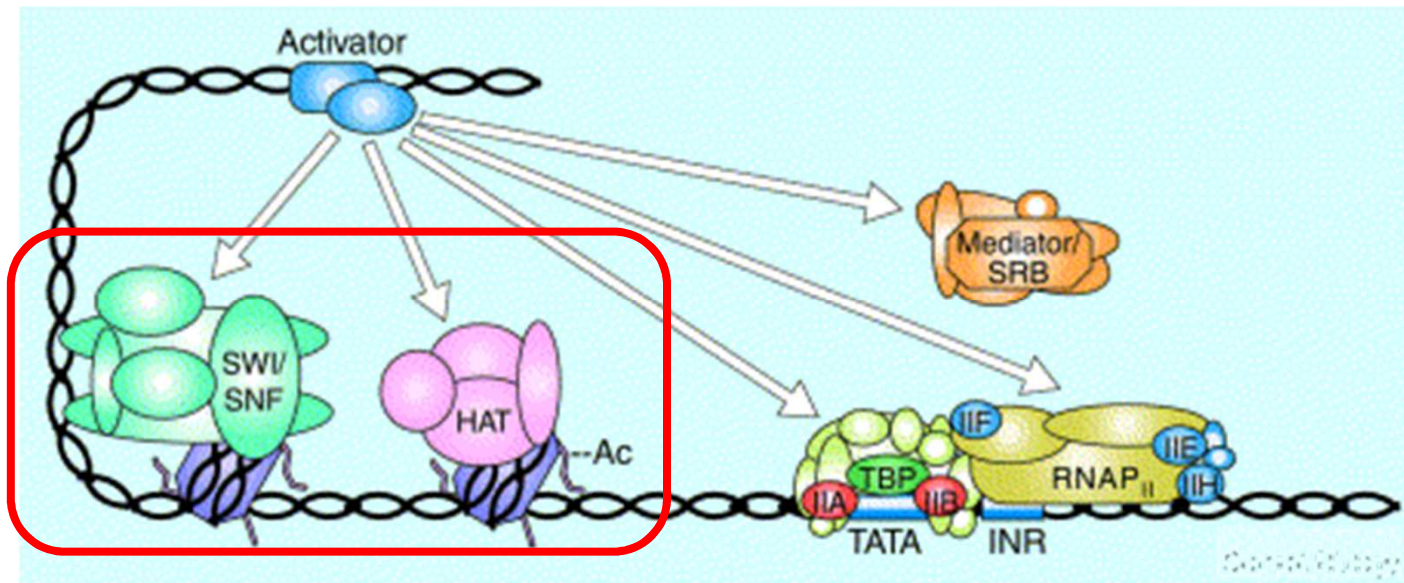


Rôle de l'ubiquitine hydrolase USP22 dans le remodelage de la chromatine

Transcription co-activator complexes



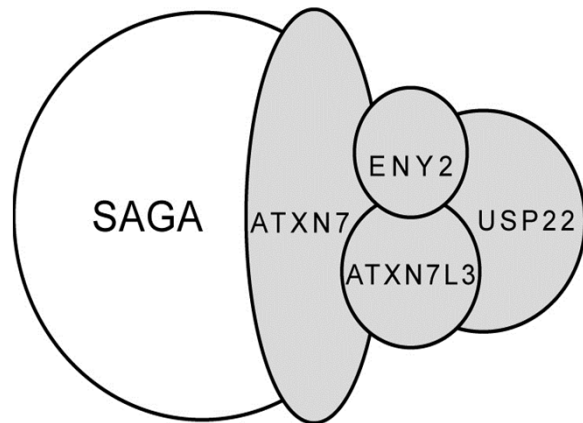
Coactivator complexes

Remodelling complex

Post-translational
modifications

SAGA

Identification of a deubiquitylation module of the SAGA complex

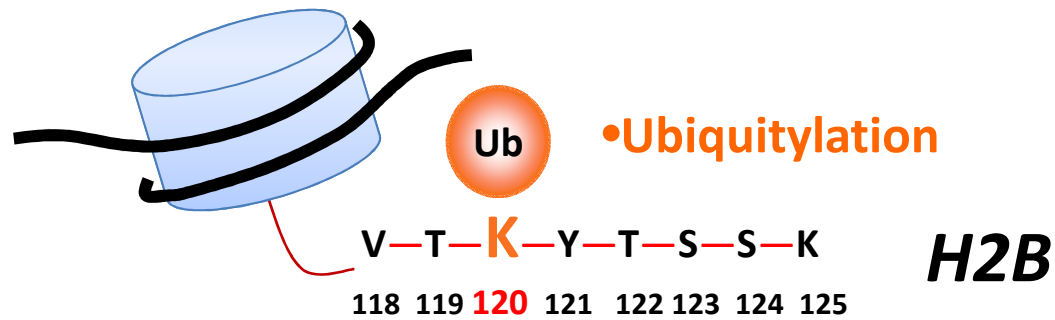
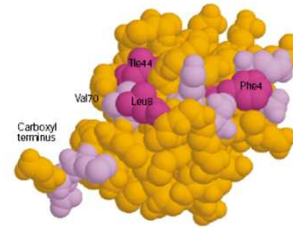


*DeUbiquitylation
of monoUb
histone H2B*

	ySAGA	hSAGA
<i>HAT module</i>	Gcn5	GCN5
	Ada3	ADA3
	Ada2	ADA2b
	Sgf29	SGF29
<i>DUB module</i>	Ubp8	USP22
	Sgf73	ATXN7
	Sgf11	ATXN7L3
	Sus1	ENY2
<i>Link activators</i>	Tra1	TRRAP
<i>Core SAGA</i>	TAF5	TAF5L
	TAF6	TAF6L
	TAF9	TAF9
	Ada1	ADA1
	TAF12	TAF12
	Spt7	SPT7L
	TAF10	TAF10
	Spt3	SPT3
	Spt8	?
	Spt20	SPT20

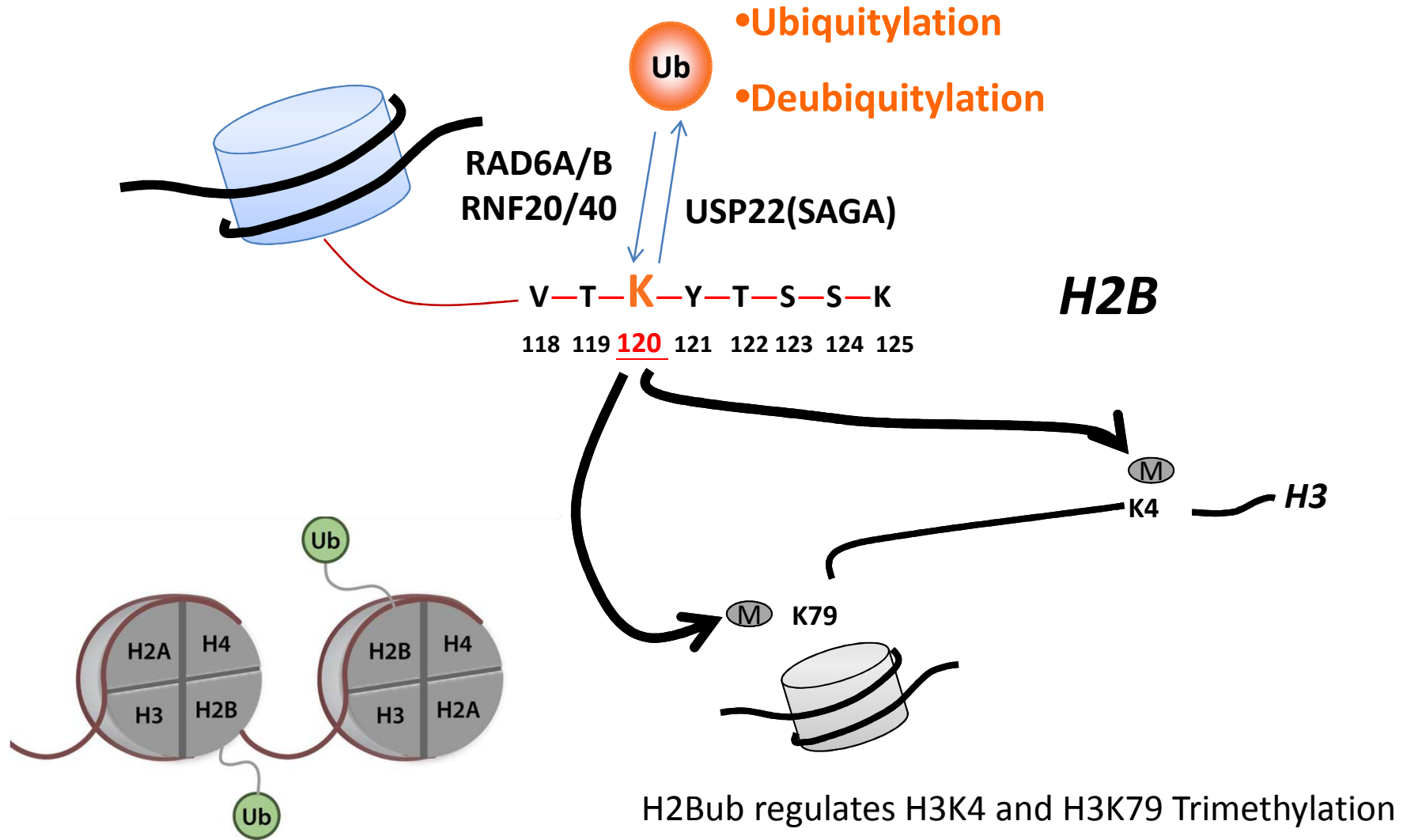
H2B ubiquitylation (H2Bub)

- At the C-tail of H2B: Lysine120 in human
- Ubiquitin: 76 amino acids



(Hicke L, 2001)

Regulation of H2B ubiquitylation



H2Bub, DNA repair and tumorigenesis

Molecular Cell
Article

Requirement of ATM-Dependent Monoubiquitylation of Histone H2B for Timely Repair of DNA Double-Strand Breaks

Lilach Moyal,^{1,11} Yaniv Lerenthal,^{1,11} Mali Gana-Weisz,¹ Gilad Mass,¹ Sairei So,² Shih-Ya Wang,² Berina Eppink,³ Young Min Chung,⁴ Gil Shalev,¹ Efrat Shema,⁵ Dganit Shkedy,¹ Nechama I. Smorodinsky,⁶ Nicole van Vliet,³ Bernhard Kuster,⁷ Matthias Mann,⁸ Aaron Ciechanover,⁹ Jochen Dahm-Daphi,¹⁰ Roland Kanaar,³ Mickey C.-T. Hu,⁴ David J. Chen,² Moshe Oren,⁵ and Yosef Shiloh^{1,*}

Regulation of Homologous Recombination by RNF20-Dependent H2B Ubiquitination

Kyosuke Nakamura,^{1,5} Akihiro Kato,^{1,5} Junya Kobayashi,¹ Hiromi Yanagihara,¹ Shuichi Sakamoto,¹ Douglas V.N.P. Oliveira,¹ Mikio Shimada,¹ Hiroshi Tauchi,² Hidekazu Suzuki,³ Satoshi Tashiro,³ Lee Zou,⁴ and Kenshi Komatsu^{1,*}



The histone H2B-specific ubiquitin ligase RNF20/hBRE1 acts as a putative tumor suppressor through selective regulation of gene expression

Efrat Shema, Itay Tirosh, Yael Aylon, *et al.*

Genes & Dev. 2008 22: 2664-2676

Access the most recent version at doi:[10.1101/gad.1703008](https://doi.org/10.1101/gad.1703008)

H2Bub and tumorigenesis



Related Commentary, page 1463  Research article

Microarray analysis identifies a death-from-cancer signature predicting therapy failure in patients with multiple types of cancer

Gennadi V. Glinsky, Olga Berezovska, and Anna B. Glinskii

Table 3

The 11-gene signature associated with poor prognosis of cancer patients diagnosed with multiple types of cancer

Gene	UniGene ^A (<i>Homo sapiens</i>)	Affymetrix MG-U74A probe set	GenBank accession no.	UniGene ^A (<i>Mus musculus</i>)
<i>Gbx2</i>	Hs.184945	94200_at	Z48800	Mm.204730
<i>KI67</i>	Hs.80976	99457_at	X82786	Mm.4078
<i>CCNB1</i>	Hs.23960	160159_at	X64713	Mm.318364
<i>BUB1</i>	Hs.469649	104097_at	AF002823	Mm.2185
<i>KNTC2</i>	Hs.414407	93441_at	AI595322	Mm.225956
<i>USP22</i>	Hs.462492	97960_at	AW125800	Mm.30602
<i>HCFC1</i>	Hs.83634	100901_at	U80821	Mm.248353
<i>RNF2</i>	Hs.124186	93164_at	Y12783	Mm.31512
<i>ANK3</i>	Hs.499725	98477_s_at	L40632	Mm.235960
<i>FGFR2</i>	Hs.533683	93090_at	M23362	Mm.16340
<i>CES1</i>	Hs.499222	101538_i_at	AW226939	Mm.292803

^AUniGene IDs were updated to correspond with the UniGene cluster IDs in build 183 (NCBI UniGene website; <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=unigene>).

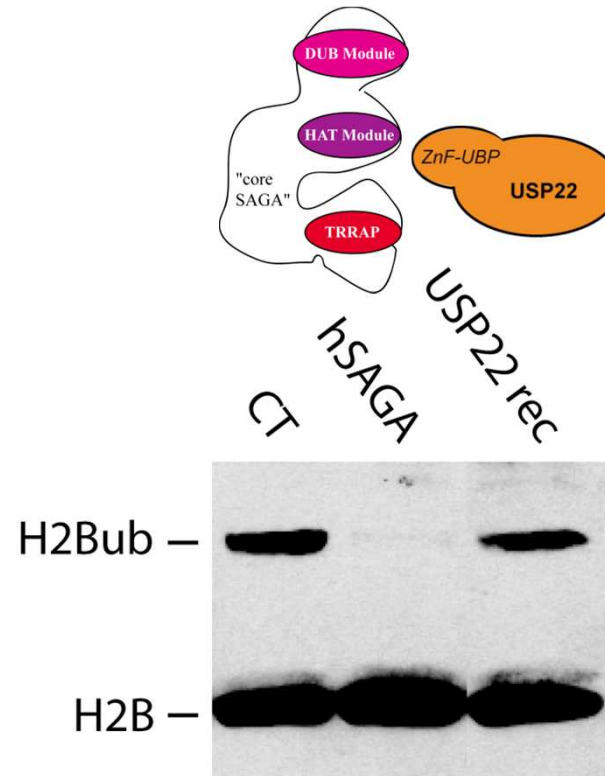
11 gene signature:

- cancer stem cell phenotype
- poor prognosis and death after treatment

USP22 : H2Bub deubiquitylase

Bmi1 and Ring1B : subunits of PRC1 repressive complex mediates H2Aub

Deubiquitylation activity of USP22 and SAGA



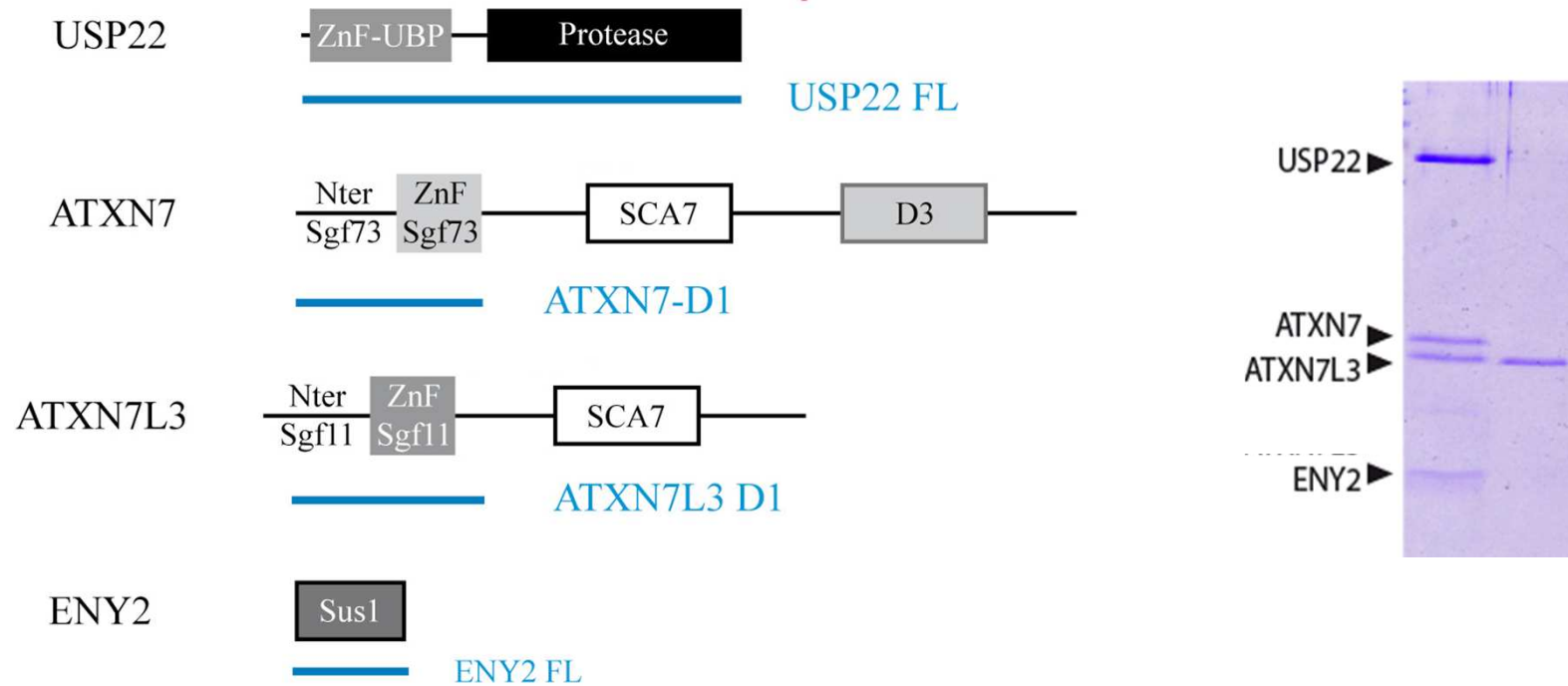
How is USP22 regulated ?

USP22



Domains required to activate USP22 ?

Reconstitution of a recombinant DUB module



Domains required to activate USP22 ?

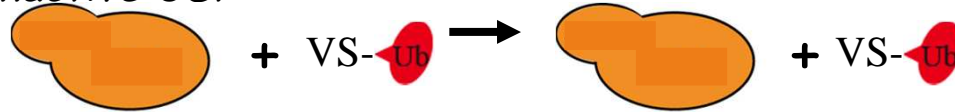
In vitro DUB assay

Suicide Substrate Ubiquitin Vinyl Sulfone (Ub-VS)

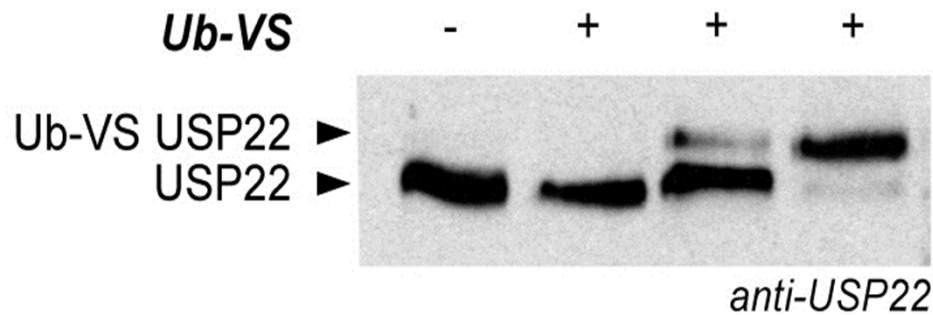
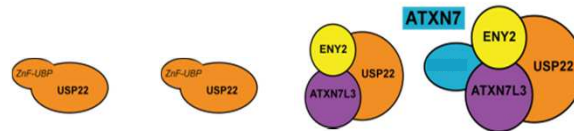
active USP



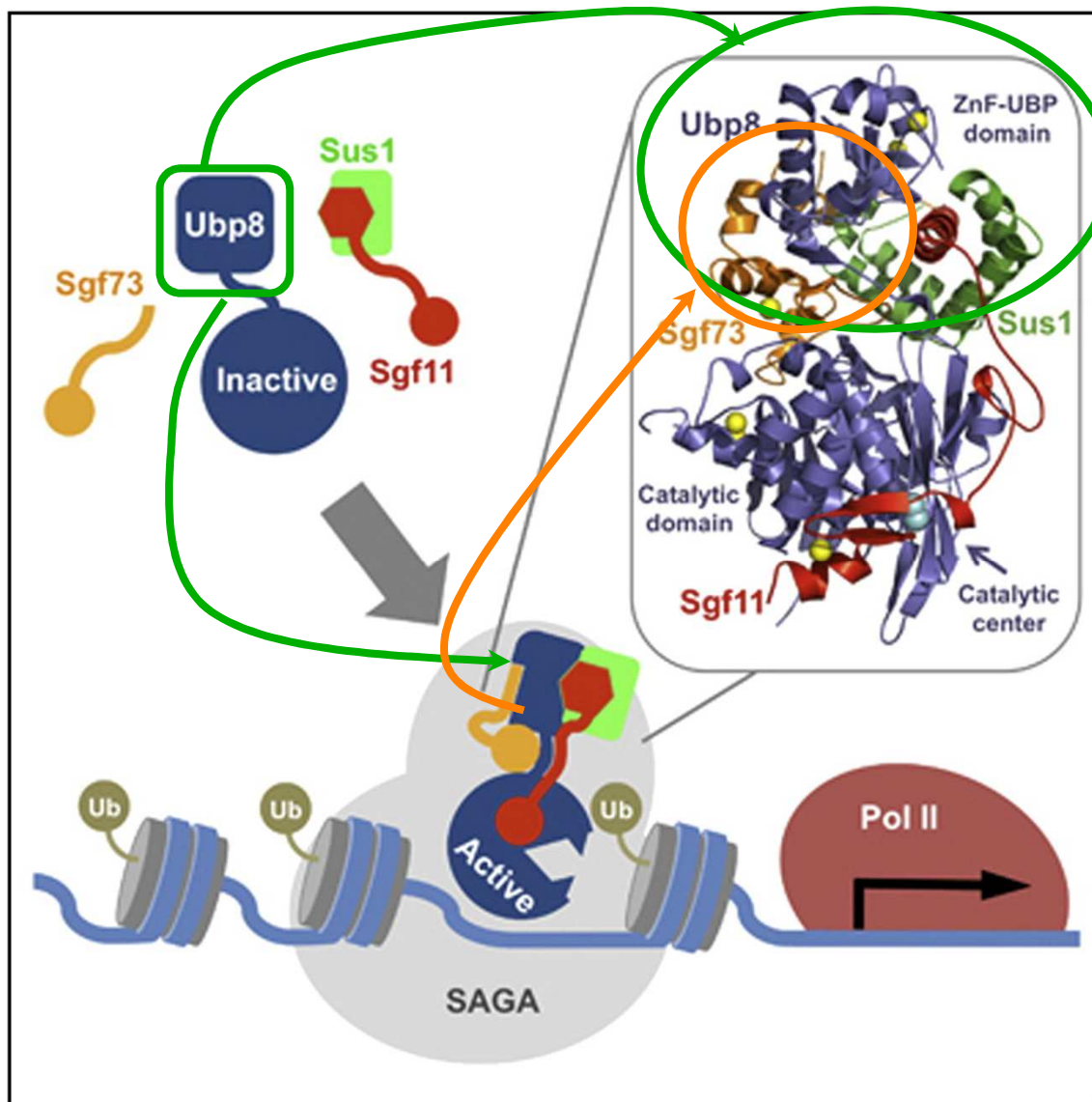
inactive USP



Covalent linkage >> shift in WB (~7kDa)



Structure of the yeast DUB module

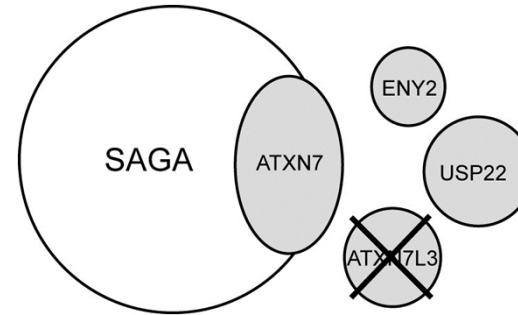
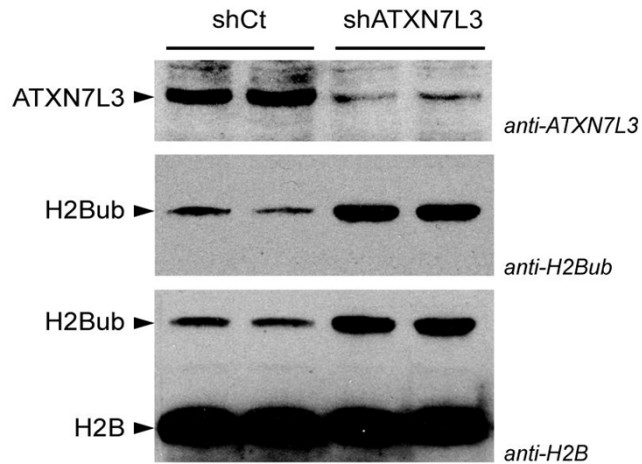


- **Ubp8 ZnF-UBP (USP22):** strong interactions with 3 other subunits = **Assembly Lobe**

- **Sgf73 D1 (ATXN7):** crucial to **position** the **assembly lobe** and the **catalytic lobe** in a **good orientation**

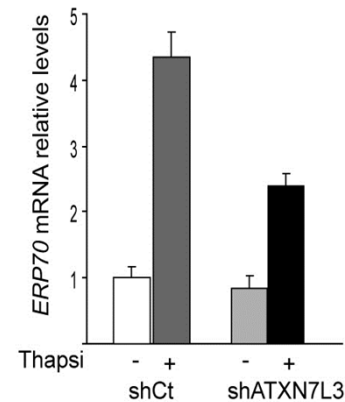
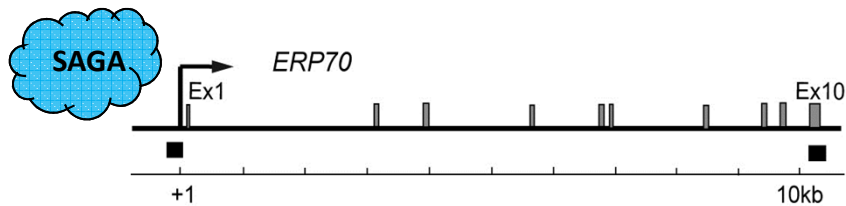
Kohler et al, Cell 2010
Samara et al, Science 2010

In vivo substrates of SAGA DUB activity



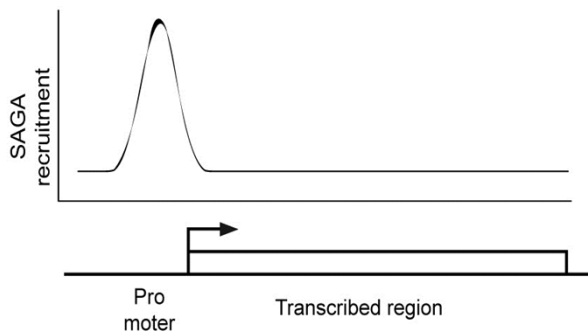
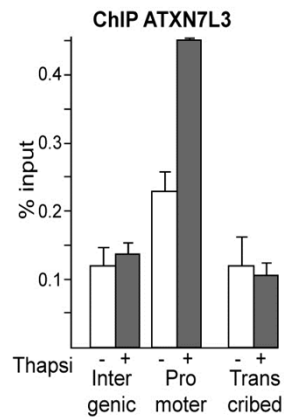
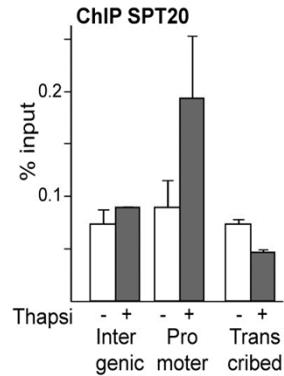
Specific inactivation of the SAGA DUB activity after ATXN7L3 knockdown

SAGA-dependent gene : ER stress gene expression can be induced by thapsigargin



SAGA DUB activity is required for the optimal induction of SAGA-dependent gene expression

Role of SAGA DUB activity on inducible gene expression

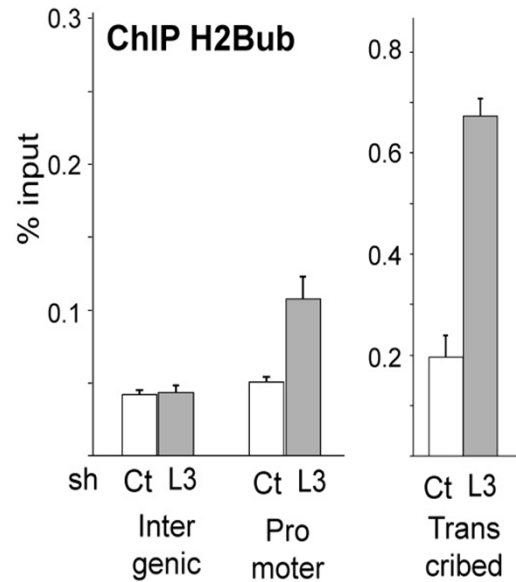


Chromatin Immuno-precipitation (ChIP) experiments detect the enrichment of a given factor at any genomic position

- The human SAGA complex is detected at the promoter of SAGA-dependant genes upon induction

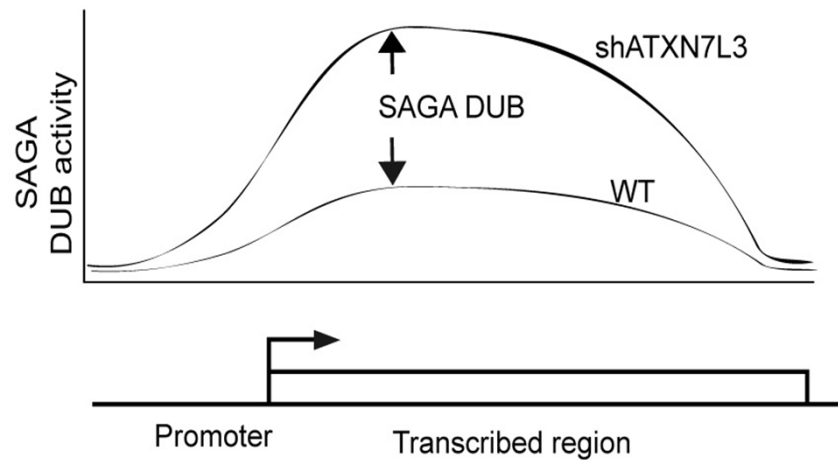
- but not in the transcribed region of these genes

Role of SAGA DUB activity on inducible gene expression



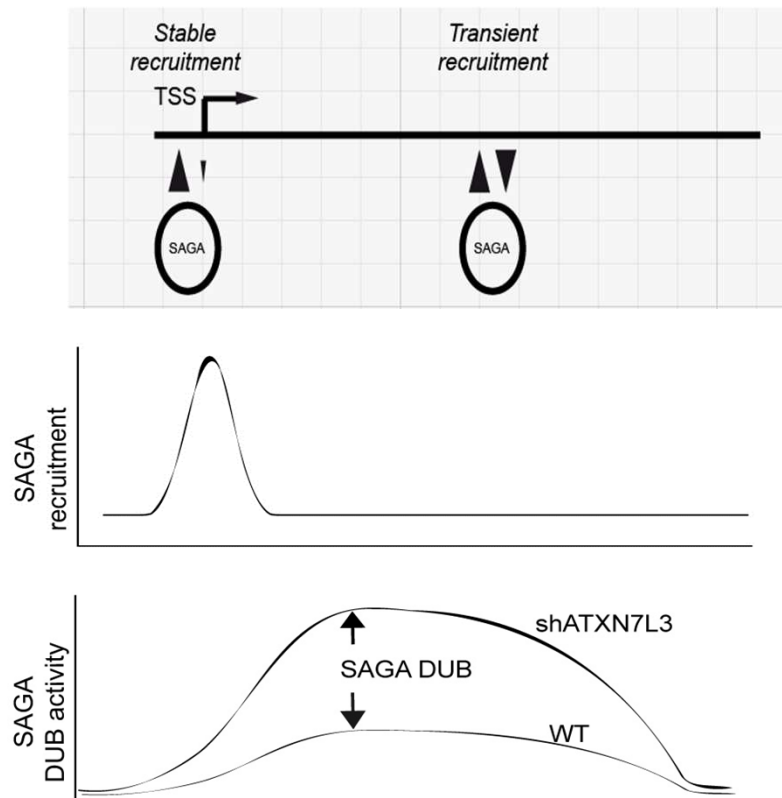
H2Bub ChIP experiments on ER stress genes:

- SAGA is recruited at the promoter region
- DUB activity of SAGA is mainly acting in the transcribed region



Conclusions

- ATXN7 and ATXN7L3 regulate the catalytic activity of USP22
- SAGA DUB activity is required for the expression of SAGA inducible genes
- The dynamics of SAGA recruitment varies in different gene regions



Difference between SAGA recruitment and activity

-ChIP-seq analysis of SAGA recruitment

-ChIP-seq analysis of H2Bub in control and shATXN7L3 cells



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