



An old transcriptional factor found a new way: CtBP promotes cancer progression by repressing autophagy

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內蒙古包頭20240714

MOLECULAR BIOLOGY INTELLIGENCE UNIT

G. Chinnadurai

CtBP Family Proteins

 Springer

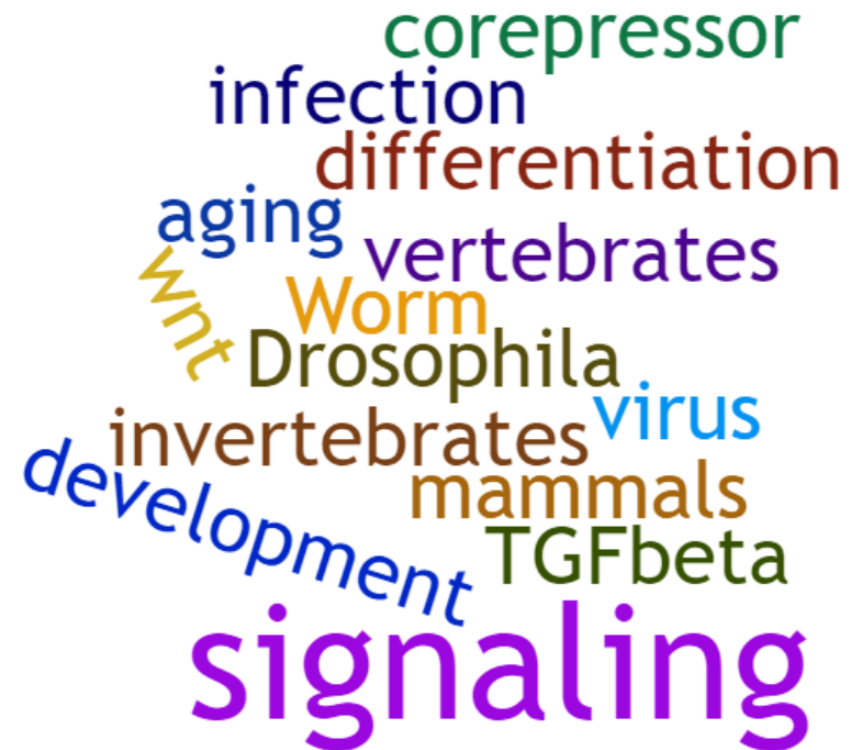
 LANDES
BIOSCIENCE

2007

Overview

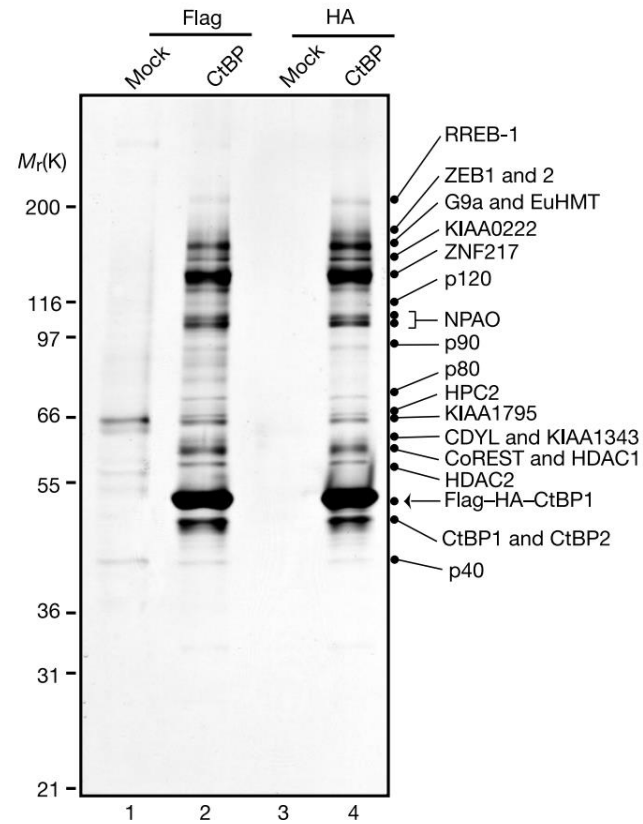
Authors: G. Chinnadurai

- Contains Chapters authored by experts in various aspects of CtBP family proteins from Drosophila, vertebrates and plants
- This is a valuable reference source for beginning and established investigators interested in CtBP

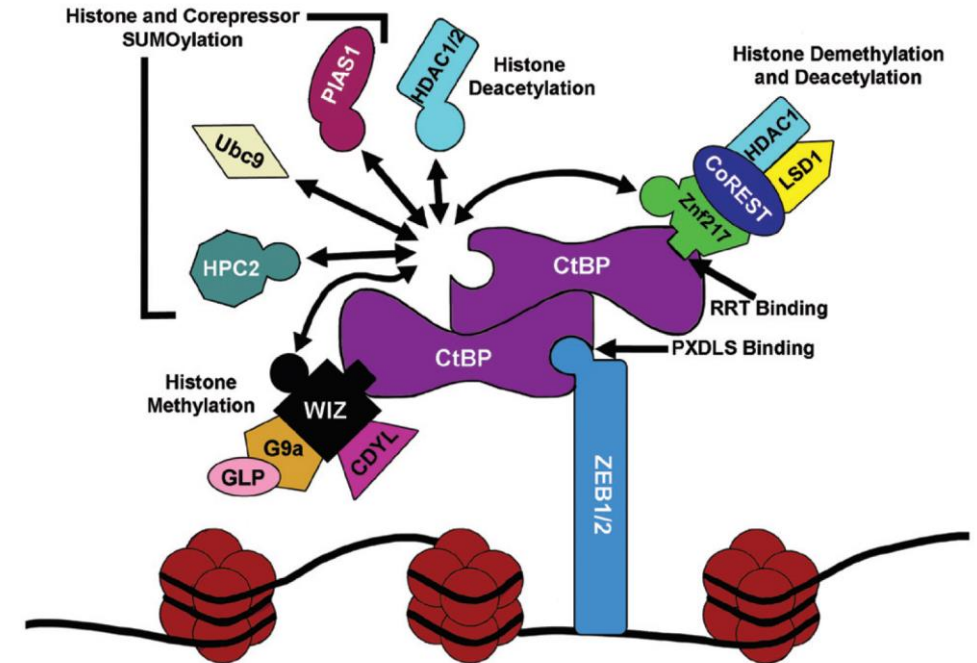


A word cloud of biological terms related to CtBP family proteins. The terms are arranged in a roughly circular pattern. The most prominent terms are 'signaling' (large purple font at the bottom), 'corepressor' (green font at the top), 'infection' (blue font), 'differentiation' (red font), 'aging' (blue font), 'vertebrates' (purple font), 'Worm' (orange font), 'Drosophila' (green font), 'virus' (blue font), 'invertebrates' (brown font), 'mammals' (orange font), 'TGFbeta' (green font), 'development' (blue font), and 'Wnt' (yellow font).

CtBP is an organizer of repressor complexes

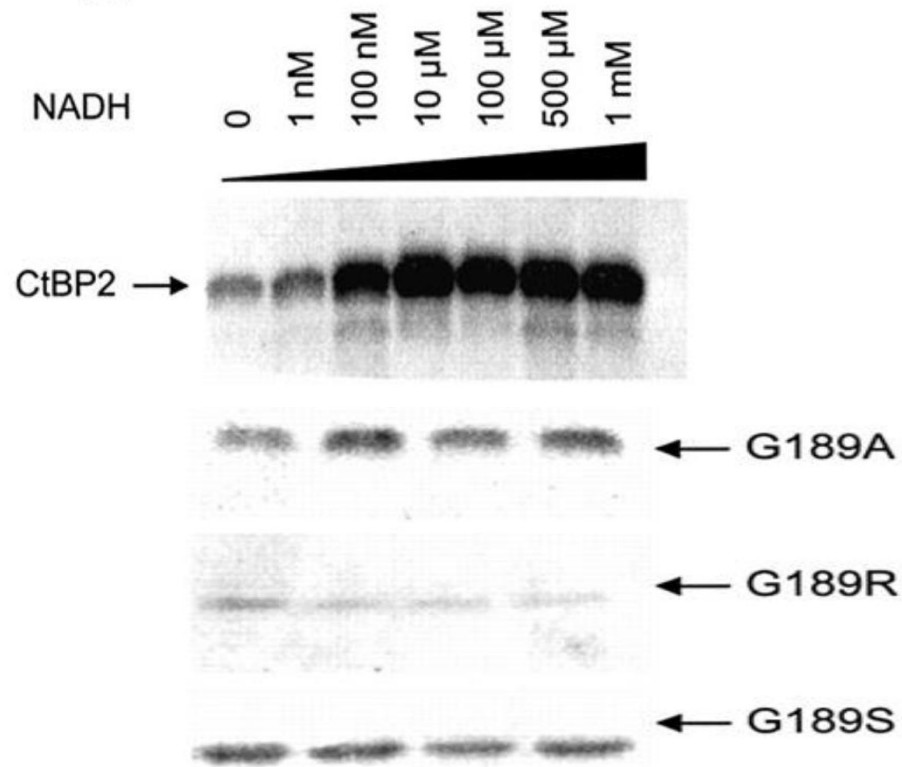


Group	CtBP-binding protein	Motif							
		1	2	3	4	5	6	7	8
D(3)K(7)	Ad2/5 E1A	P	L	D	L	S	C	K	-
	RIP140	P	I	D	L	S	C	K	-
	Knirps	P	M	D	L	S	M	K	-
	Snail	P	Q	D	L	S	L	K	-
	Consensus	P	X	D	L	S	X	K	-
D(3)R(7)	CtIP	P	L	D	L	S	D	R	-
	Ad7	P	L	D	L	S	T	R	-
	Consensus	P	X	D	L	S	X	R	-
S(3)K(7)	xTcf-3 site 1	P	L	S	L	T	T	K	-
	xTcf-3 site 2	P	L	S	L	V	T	K	-
	hTcf-4 site 1	P	L	S	L	S	L	K	-
	hTcf-4 site 2	P	L	S	L	V	T	K	-
	Hairy	P	L	S	L	V	I	K	-
	Consensus	P	X	S	L	X	X	K	-
D(3)K(8)	BKLF	P	V	D	L	T	V	N	K
	ZEB	P	L	D	L	S	L	P	K
	Consensus	P	X	D	L	S	X	X	K

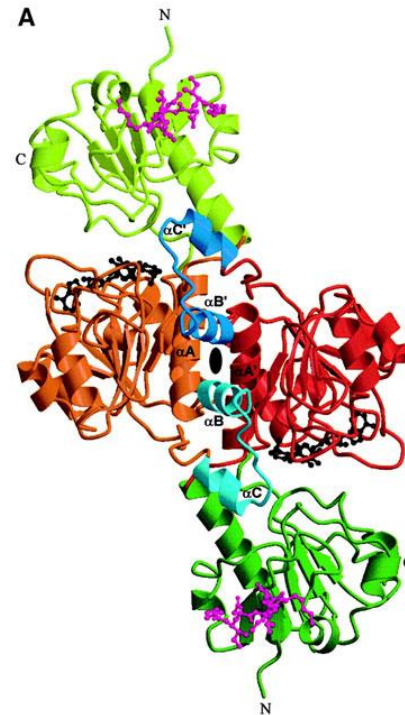


Chinnadurai et al., Mol Cell 2009
Shi et al., Nature 2003

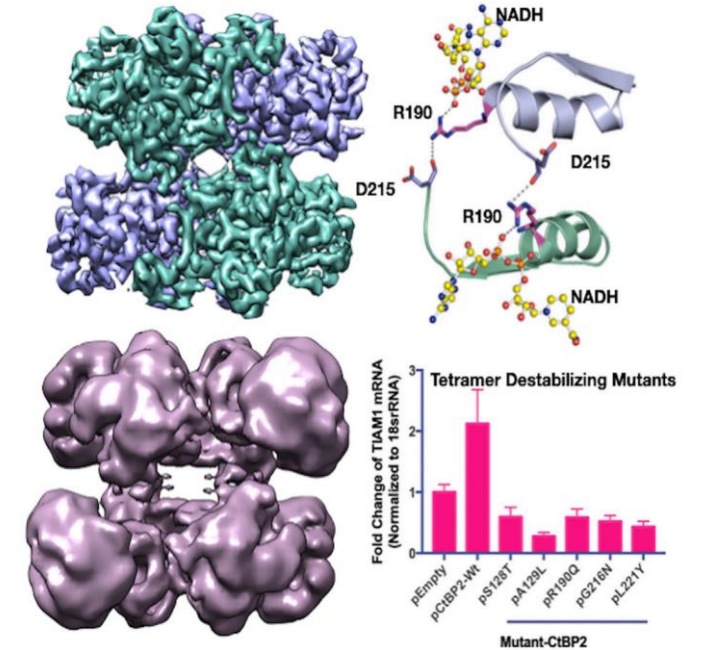
CtBP forms oligomer as functional unit



NAR 2004

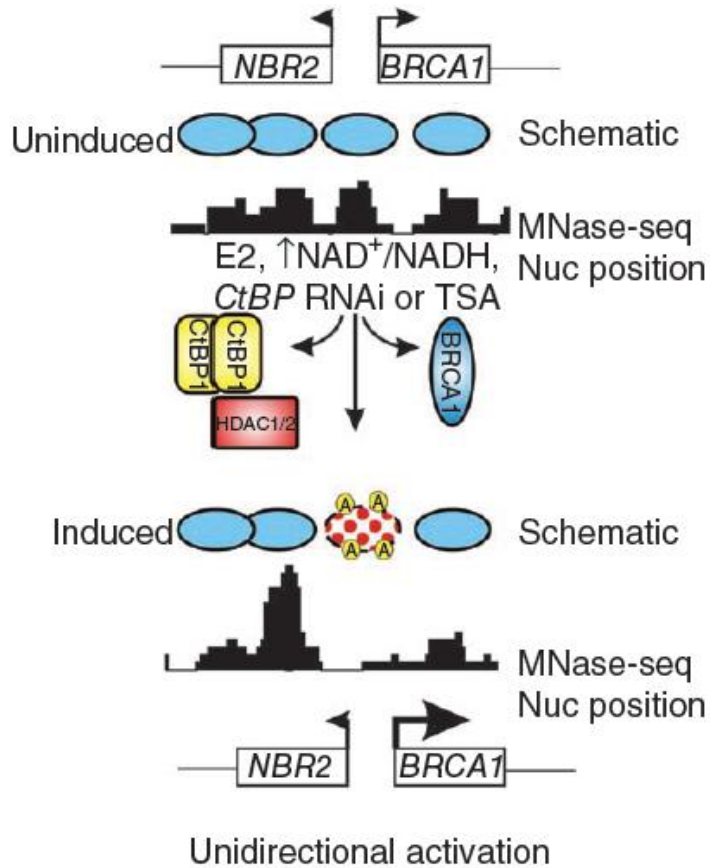


Kumar et al., MC 2002
William Royer FEBS L 2014



Bellesis et al. JBC 2018
Jacris et al. Structure 2021

CtBP is a metabolic status sensor



Regulation of corepressor function by nuclear NADH.
2002 Science

Differential binding of NAD⁺ and NADH allows the transcriptional corepressor carboxyl-terminal binding protein to serve as a metabolic sensor. *2003 PNAS*

Transcriptional regulation of *BRCA1* expression by a metabolic switch
2010 NSMB

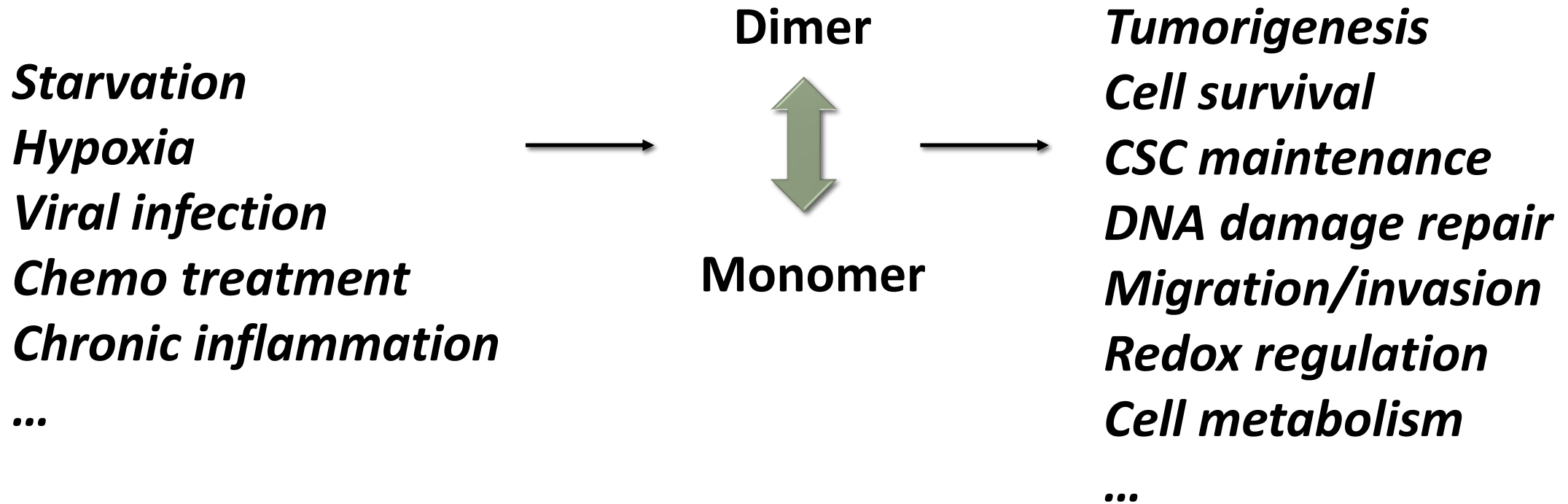
p53 is regulated by aerobic glycolysis in cancer cells by the CtBP family of NADH-dependent transcriptional regulators.
2020 Science signaling

Bioenergetic state regulates innate inflammatory responses through the transcriptional corepressor CtBP
2017 Nature Communication

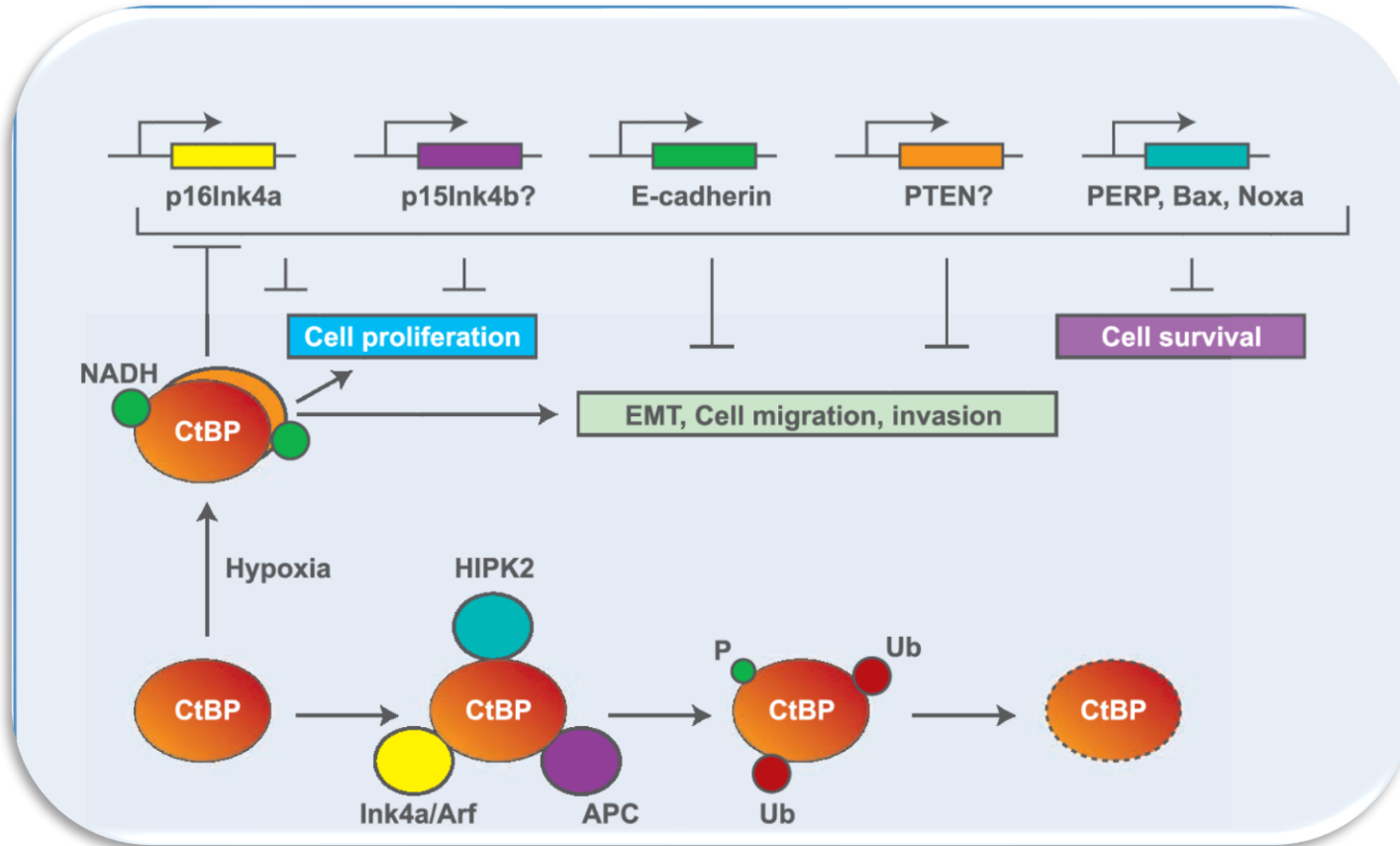
The transcriptional corepressor CtBP2 serves as a metabolite sensor orchestrating hepatic glucose and lipid homeostasis
2021 Nature Communication

2010 NSMB

Working Model



How CtBP contributes to cancer development?



Chinadurai Cancer Res 2009

BRCA1

SIRT4

SREBF2

RAD51

...

DNA damage repair

Cell cycle

Migration/invasion

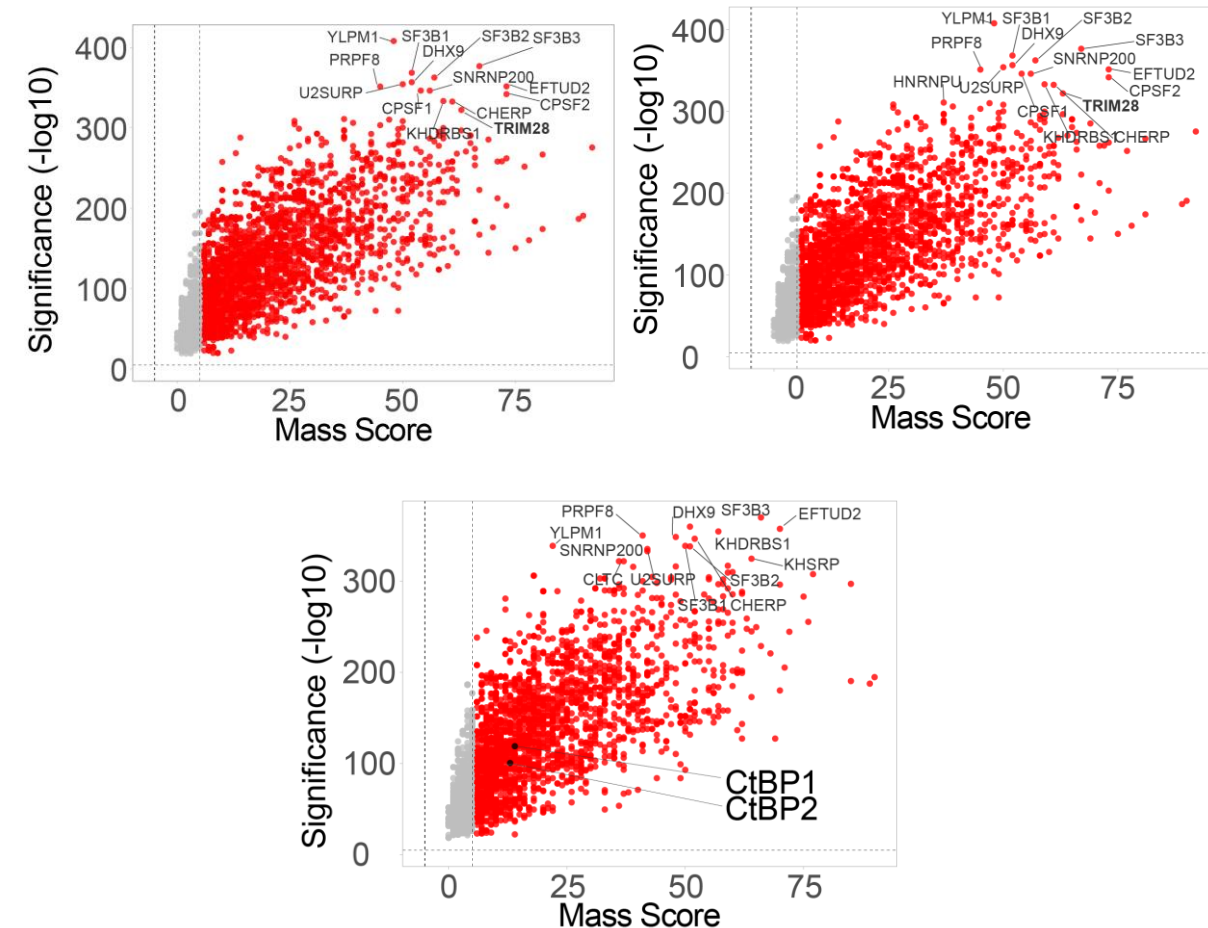
apoptosis

...

Di et al., Nature comm 2013
 Di et al., Nature Str Mol Bio 2010
 Zhao et al., Oncogene 2019
 Hao et al., CCR 2017, 2018
 Hao et al., Theranostics, 2019
 Wang et al., Cell death Disease 2015
 Wang et al., Oncogenesis 2017
 Li et al., IJBS 2023

Is it the only mechanism of CtBP function?

Bio-ID-Mass



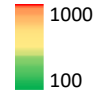
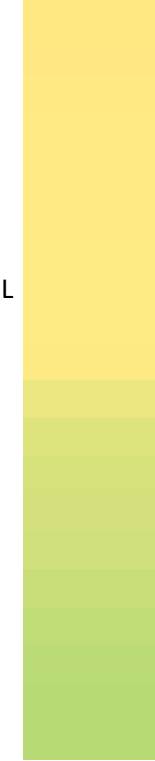
CtBP1-BioID

CRKL
AHNAK
NUP153
EIF5
PCBP1
EPB41
CORO1B
CD2AP
UBAP2
DDX42
NUMA1
TRIM28
SF3B1
TCERG1
PAPOLA
HNRNPK
TIPRL
NCL
YLPM1
HDLBP



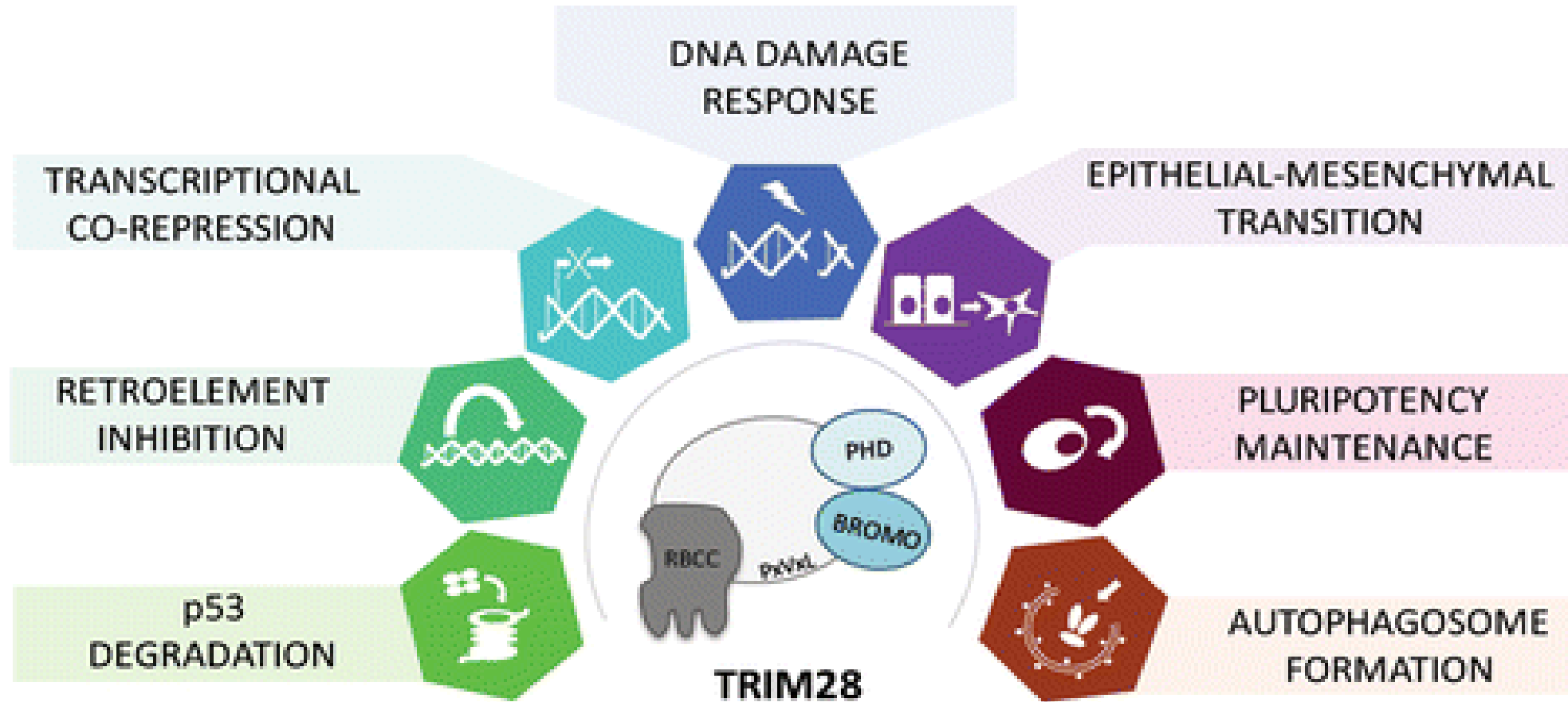
CtBP2-BioID

CAD
PTPN11
AGFG1
SLU7
ARL6IP4
EIF5
GLTSCR1
HNRNPDL
DVL2
RPL23
UBE2M
HTATSF1
UBAP2
ZC3H14
PCMT1
SUGT1
CIT
DHX8
TRIM28
NCOA2



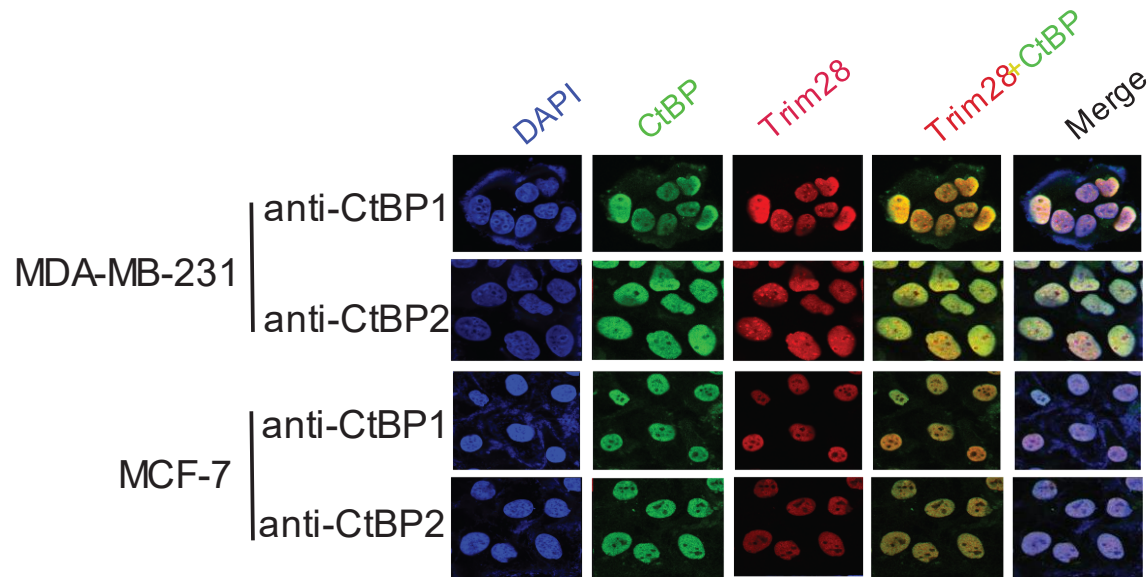
BioID analysis of CtBP1 and CtBP2 interacting proteins in MCF-7 cells.

Trim28 is a cancer related protein

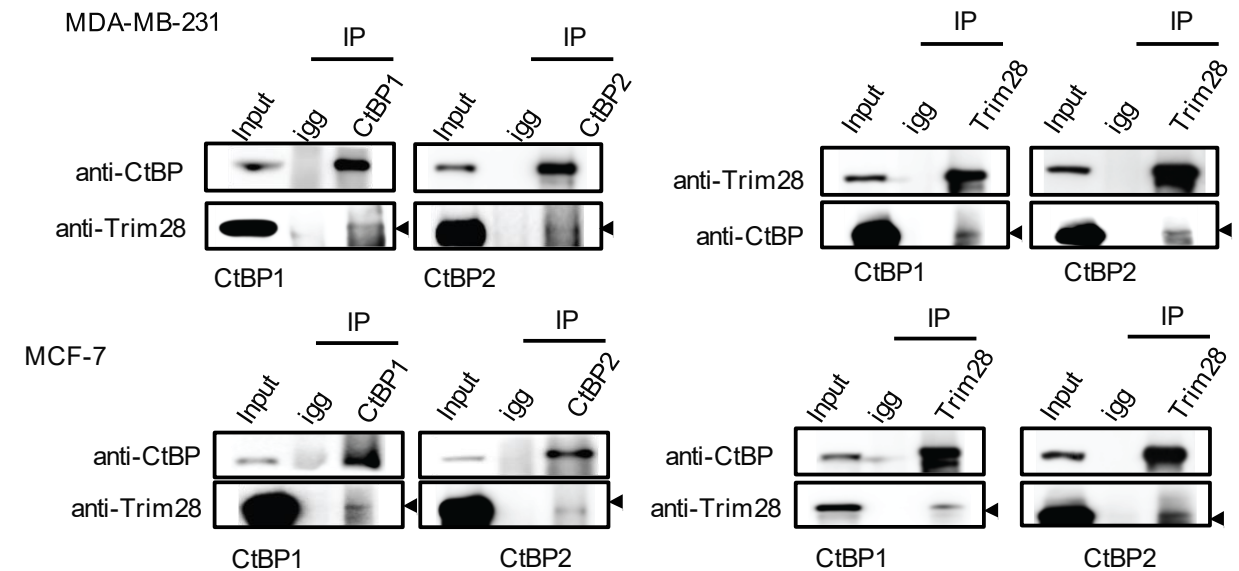


Validation of CtBP and Trim28 interaction

CtBP and Trim28 interaction: Co-localization

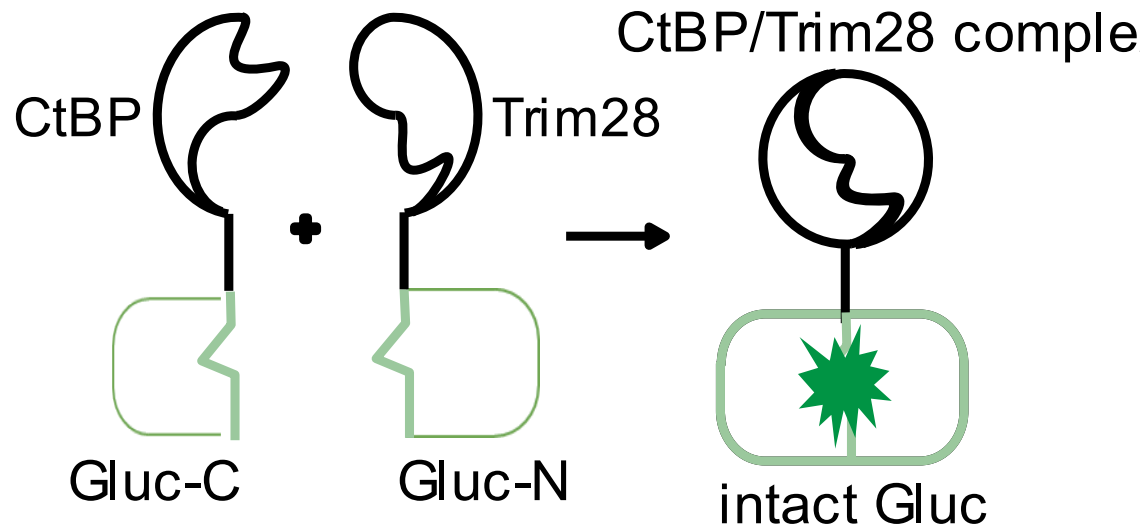


CtBP and Trim28 interaction: Co-IP

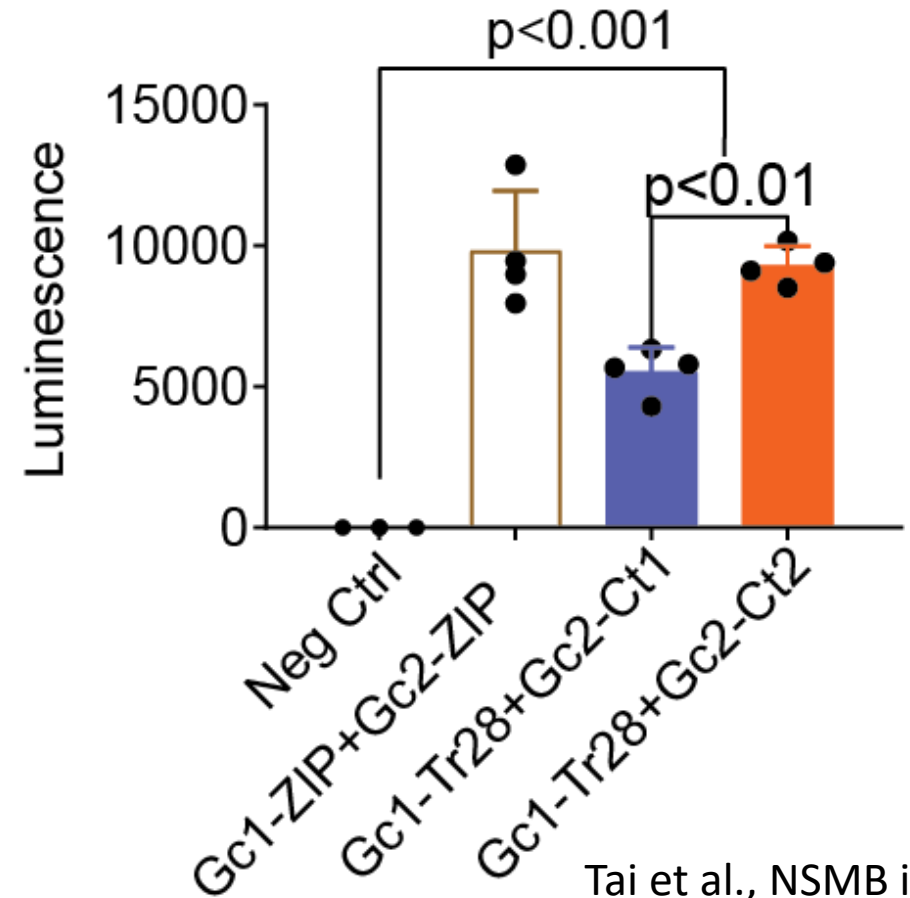


Tai et al., NSMB in revision

CtBP and Trim28 interaction: Direct vs indirect

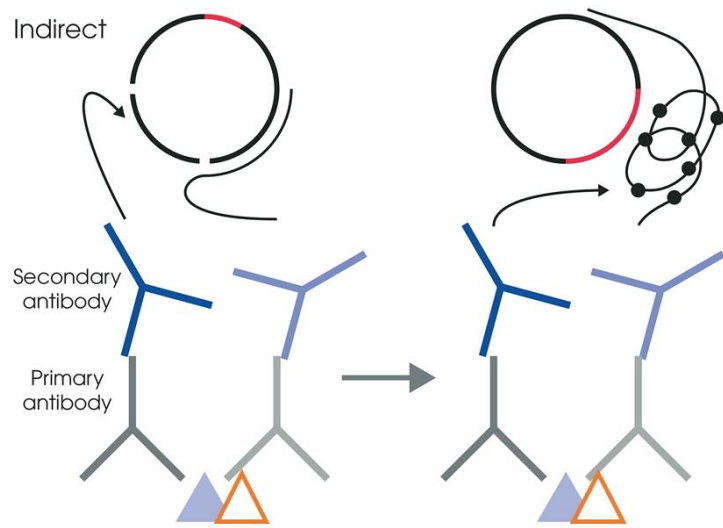


Protein complementation assay
by Gaussia luciferase

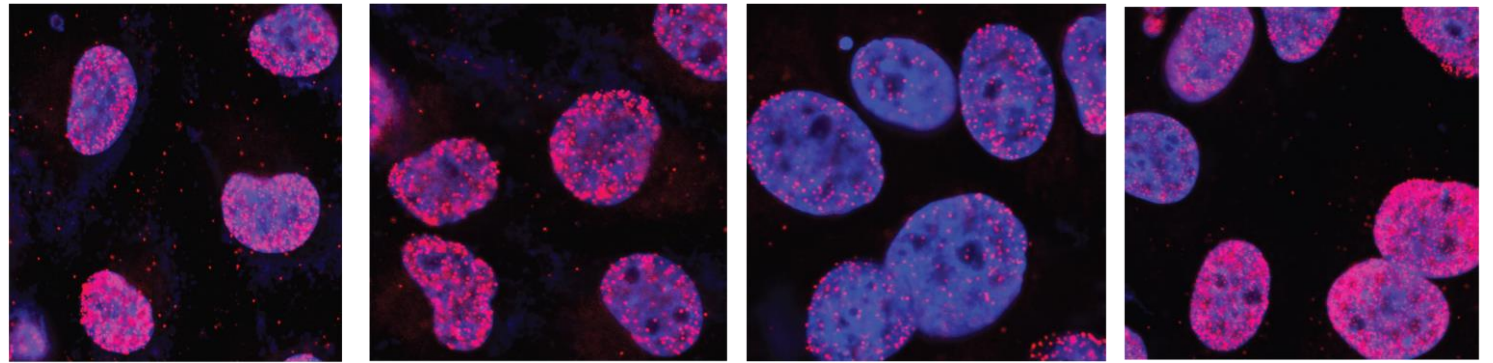


Tai et al., NSMB in revision

PLA: proximity mediated ligation assay



Blue: DAPI
Red: Ct/Tr28 PLA



Ct1

Ct2

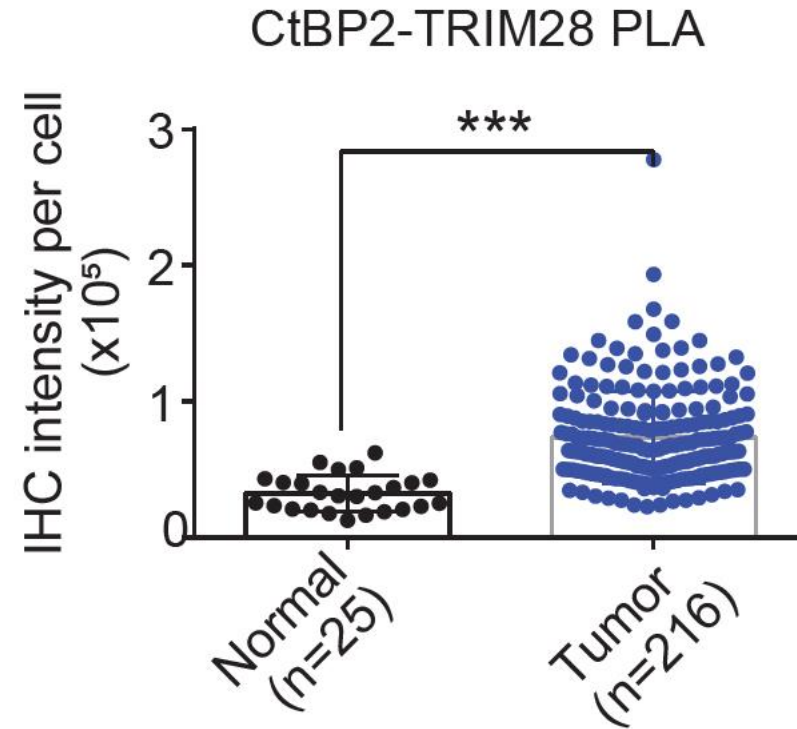
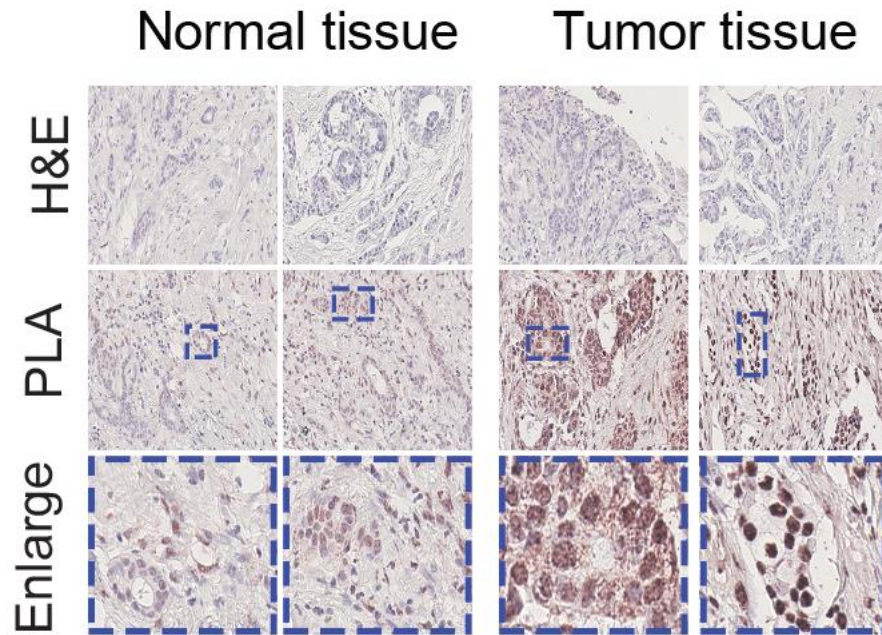
Ct1

Ct2

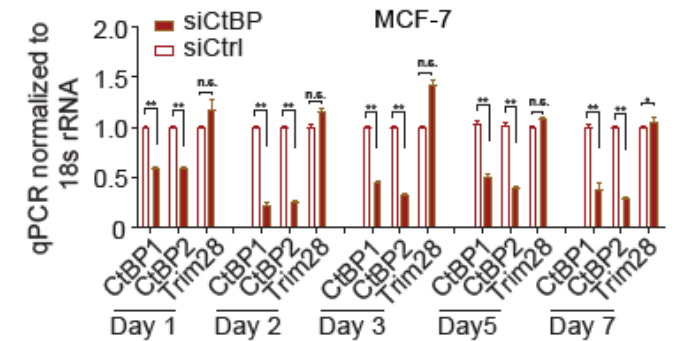
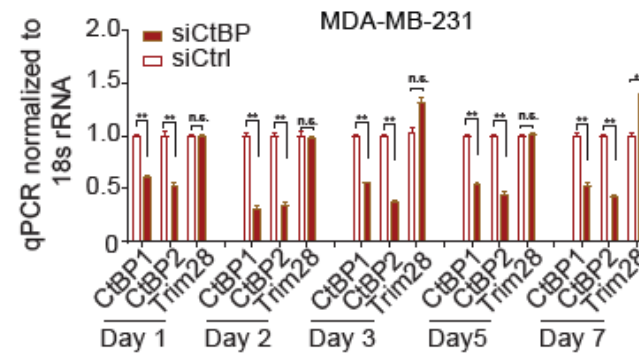
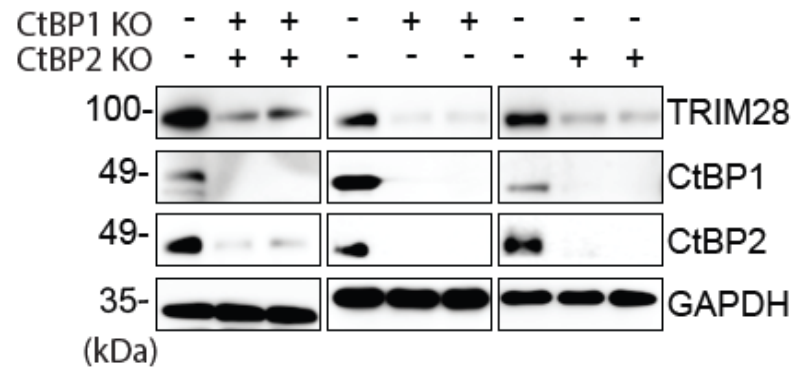
MDA-MB-231

MCF-7

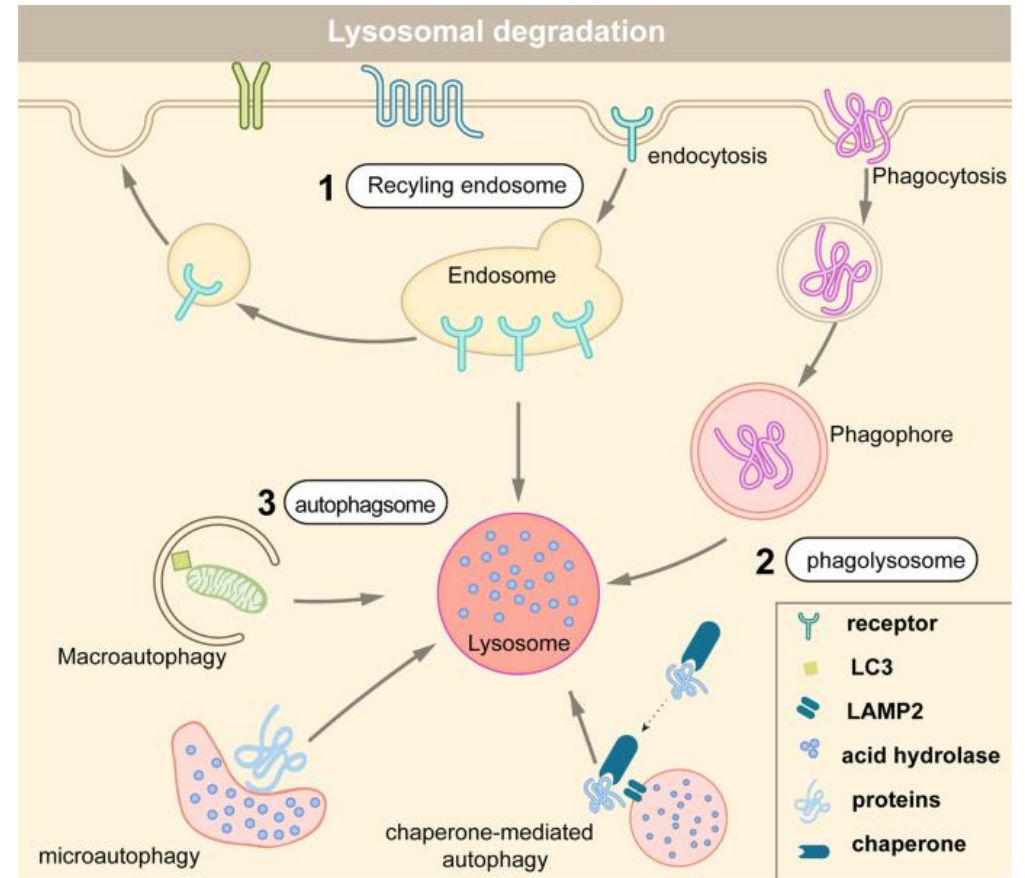
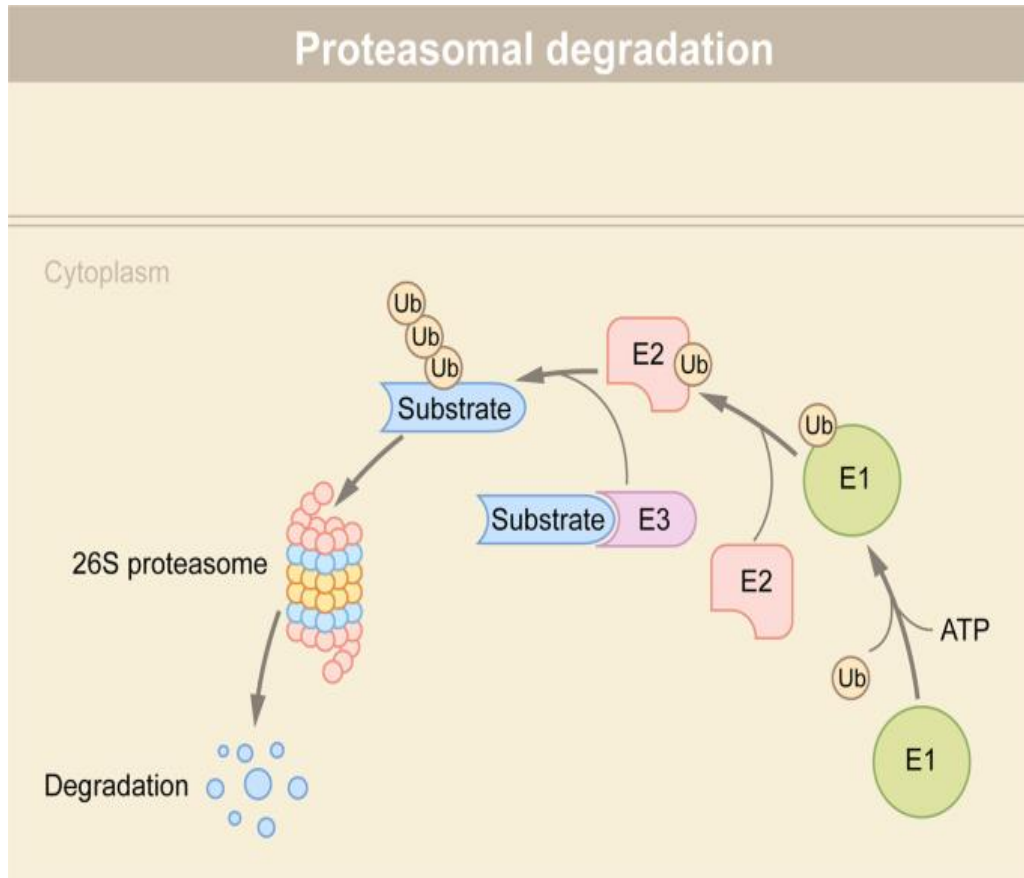
CtBP and TRIM28 interaction in Clinical Breast cancer samples



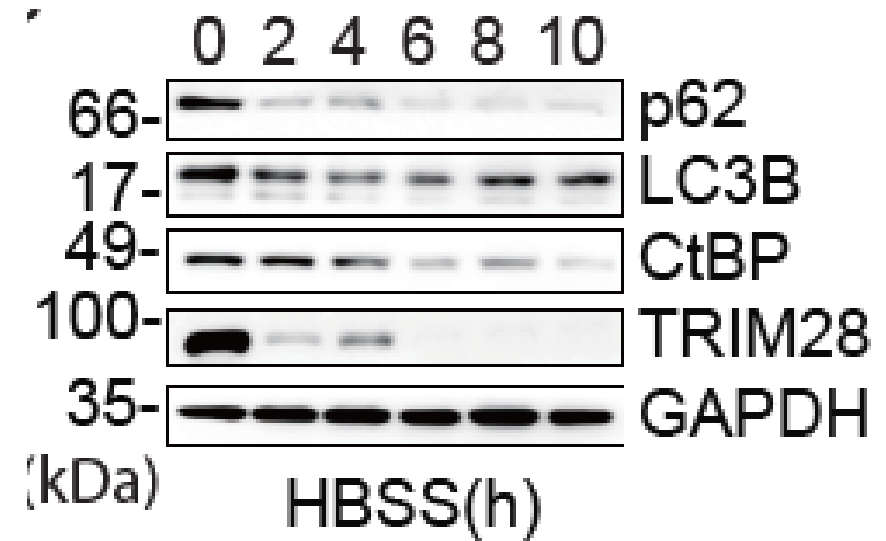
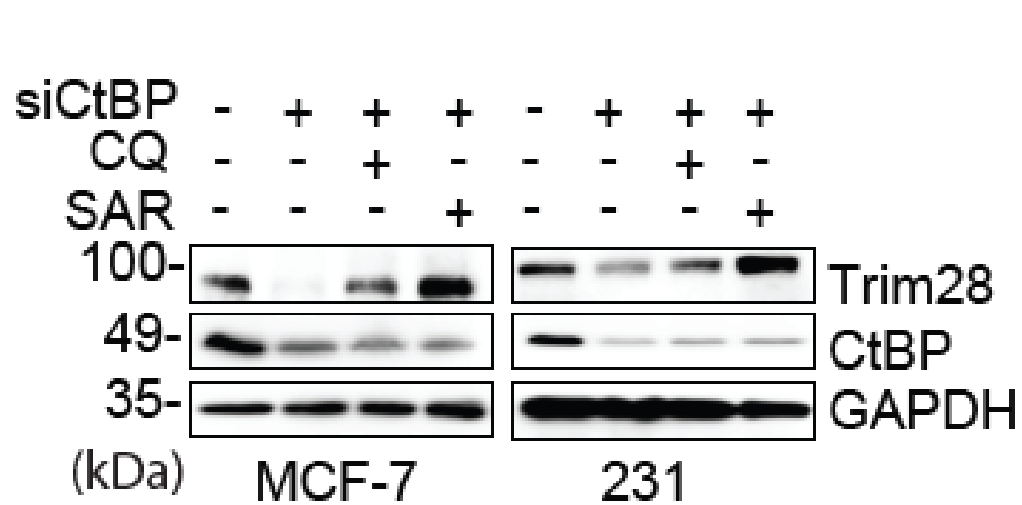
CtBP KO associates with loss of TRIM28 independent of mRNA



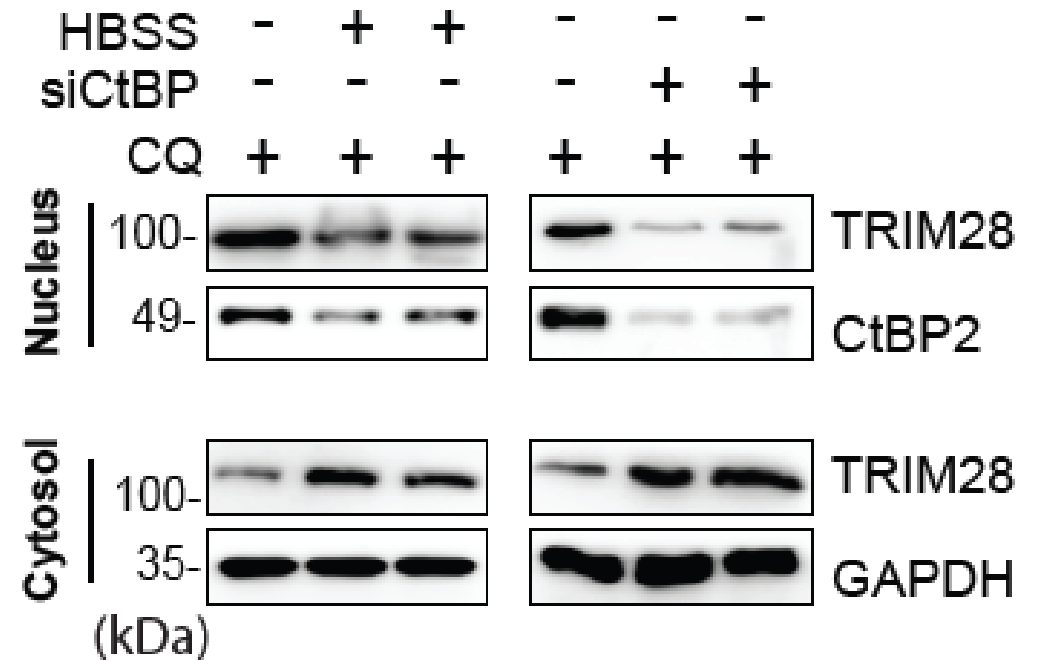
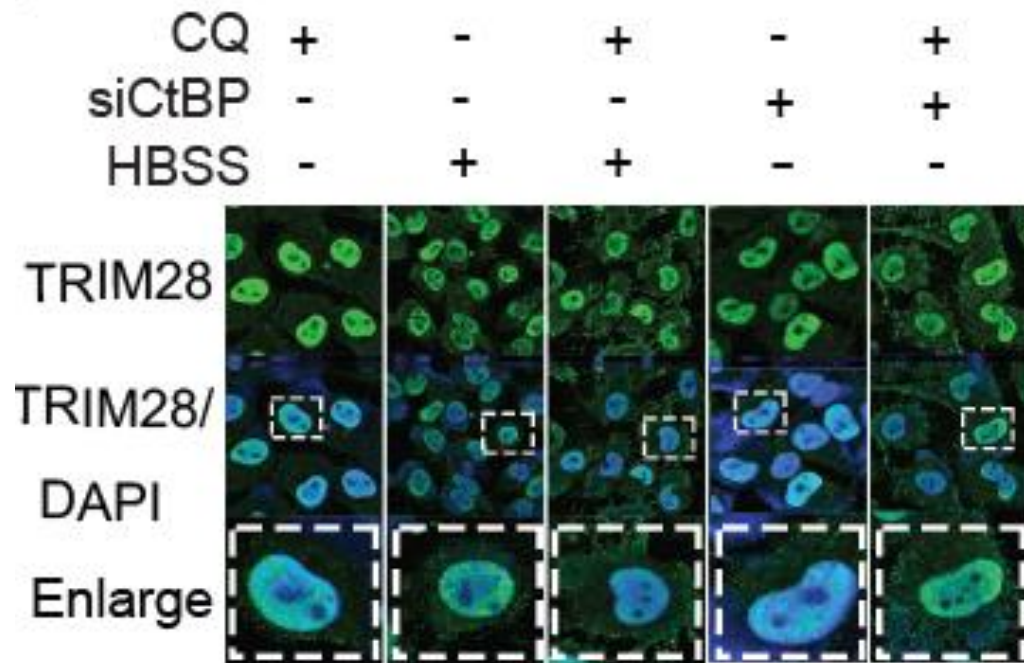
Protein degradation: Proteasome versus lysosome



TRIM28 degradation via autophagy pathway by CtBP KD/KO



Export of TRIM28 along CTBP KD or autophagy induction

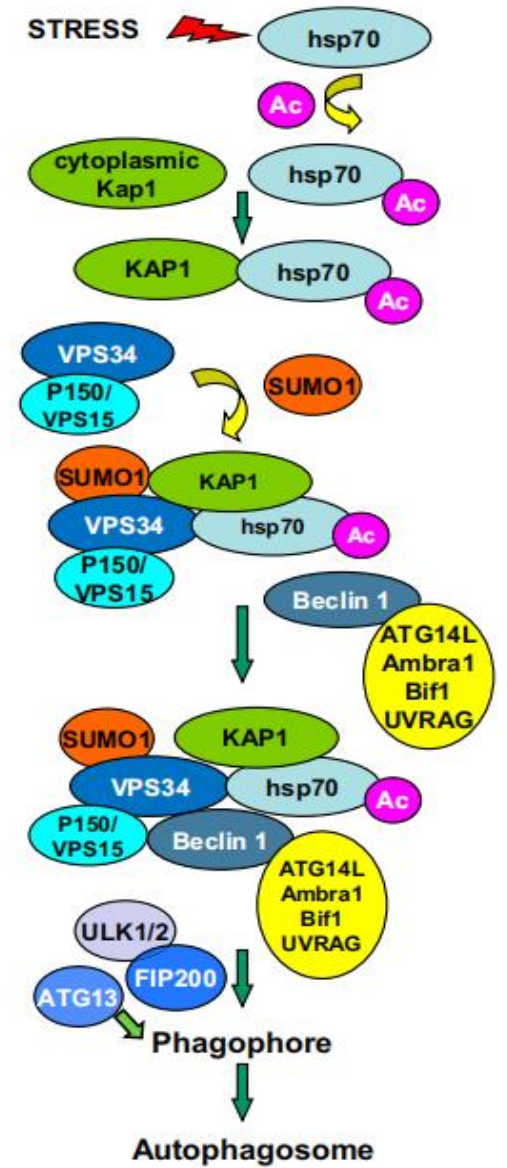
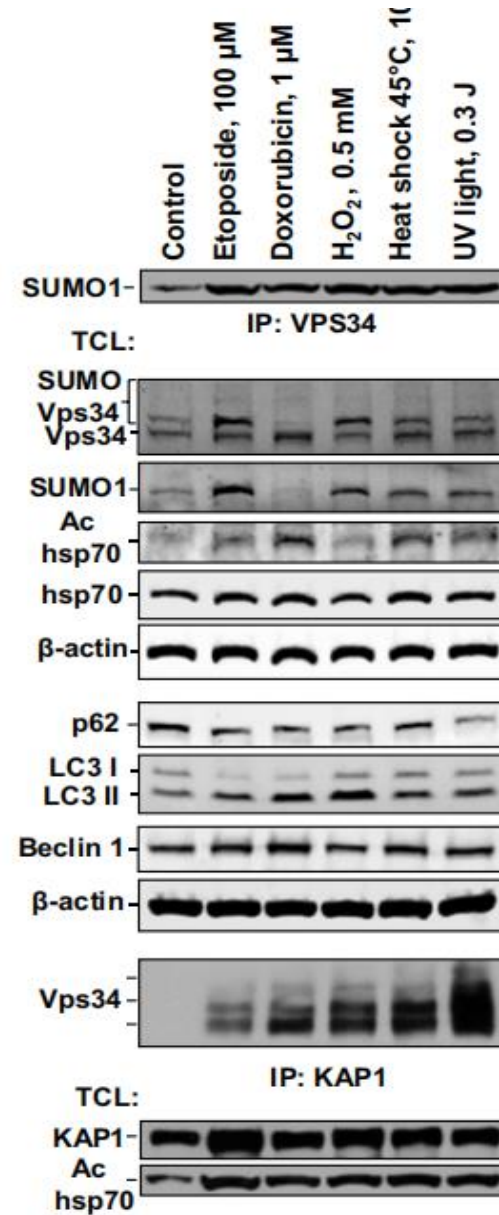


Acetylated hsp70 and KAP1-mediated Vps34 SUMOylation is required for autophagosome creation in autophagy

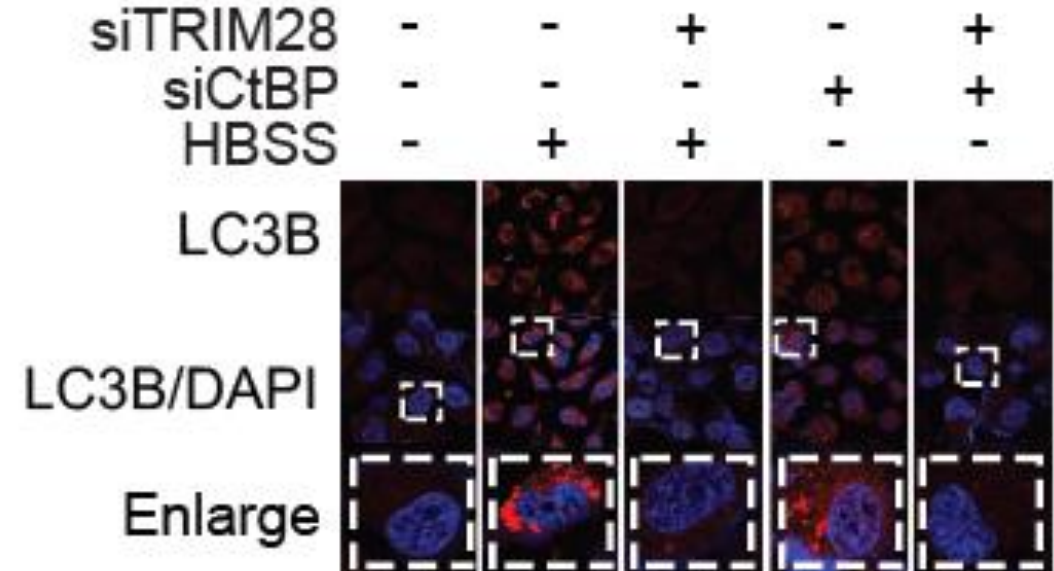
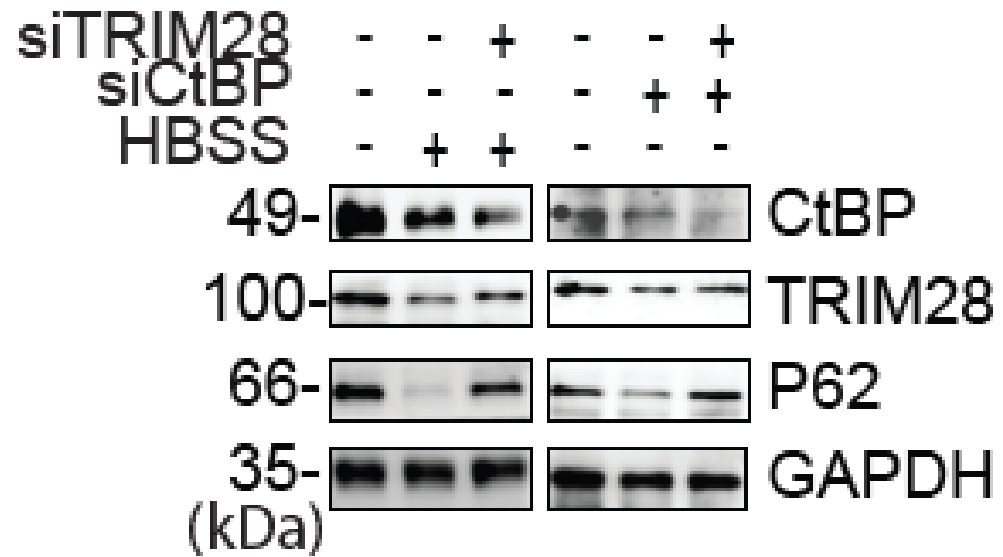
Yonghua Yang^a, Warren Fiskus^b, Bao Yong^a, Peter Atadja^c, Yoshinori Takahashi^d, Tej K. Pandita^e, Hong-Gang Wang^d, and Kapil N. Bhalla^{b,1}

^aSchool of Pharmacy, Fudan University, Shanghai 201203, China; ^bUniversity of Kansas Cancer Center, University of Kansas Medical Center, Kansas City, KS 66160; ^cOncology Drug Discovery, Novartis Institutes for Biomedical Research, Cambridge, MA 02139; ^dPenn State Hershey Cancer Institute, Hershey, PA 17033; and ^eUniversity of Texas Southwestern Medical Center, Dallas, TX 75390

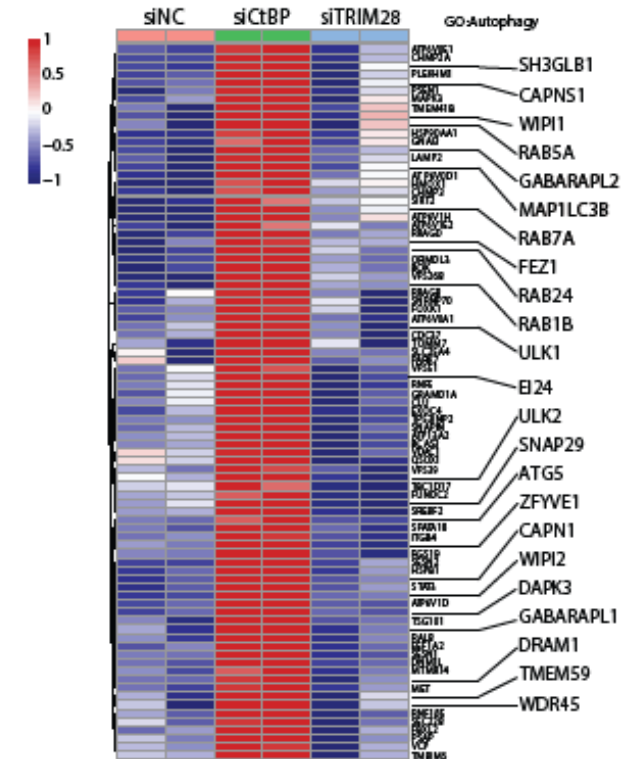
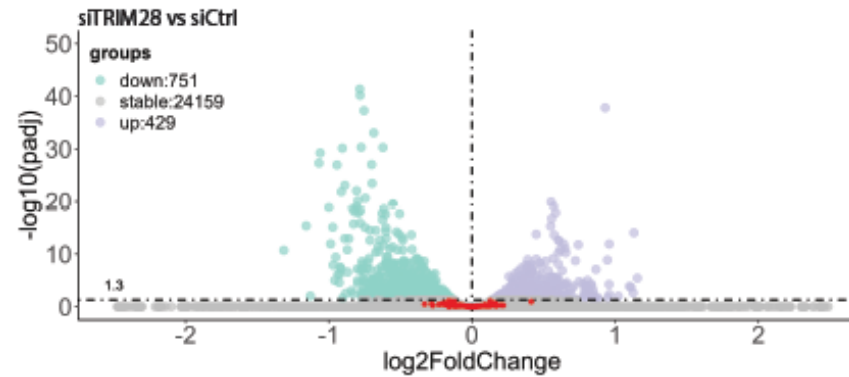
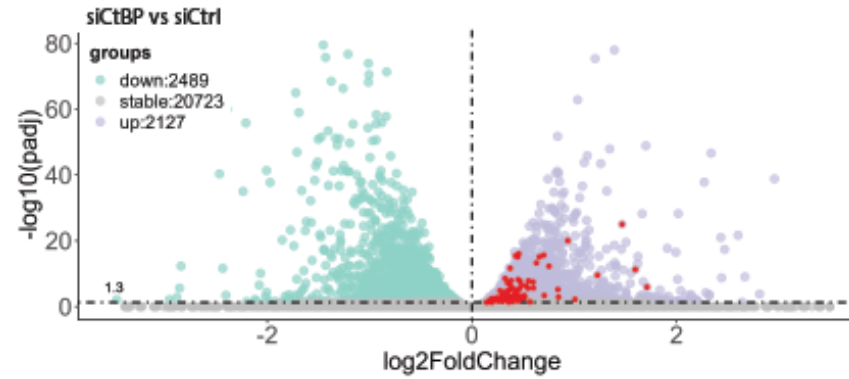
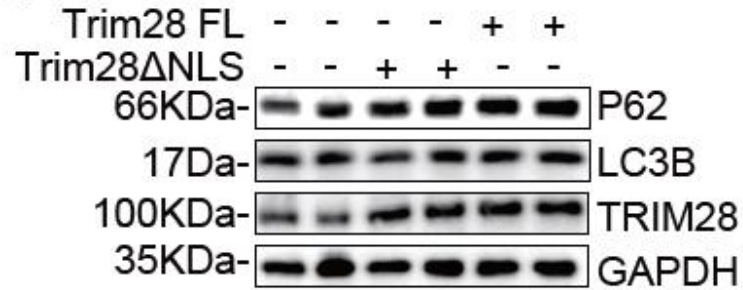
Edited by Richard A. Flavell, Howard Hughes Medical Institute, Yale School of Medicine, New Haven, CT, and approved March 12, 2013 (received for review October 10, 2012)



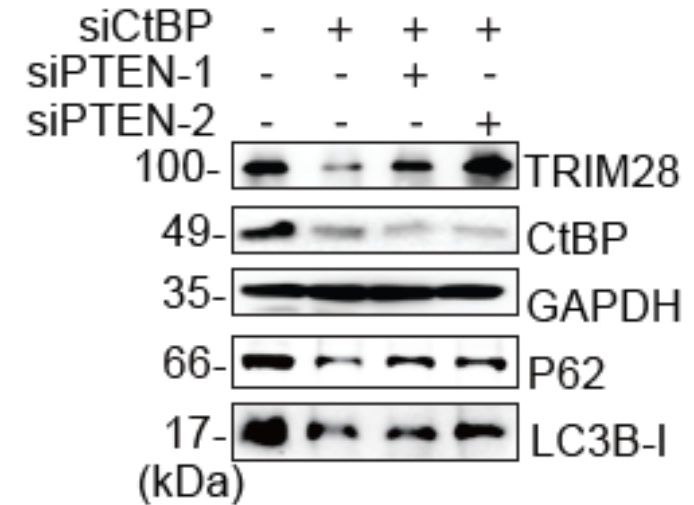
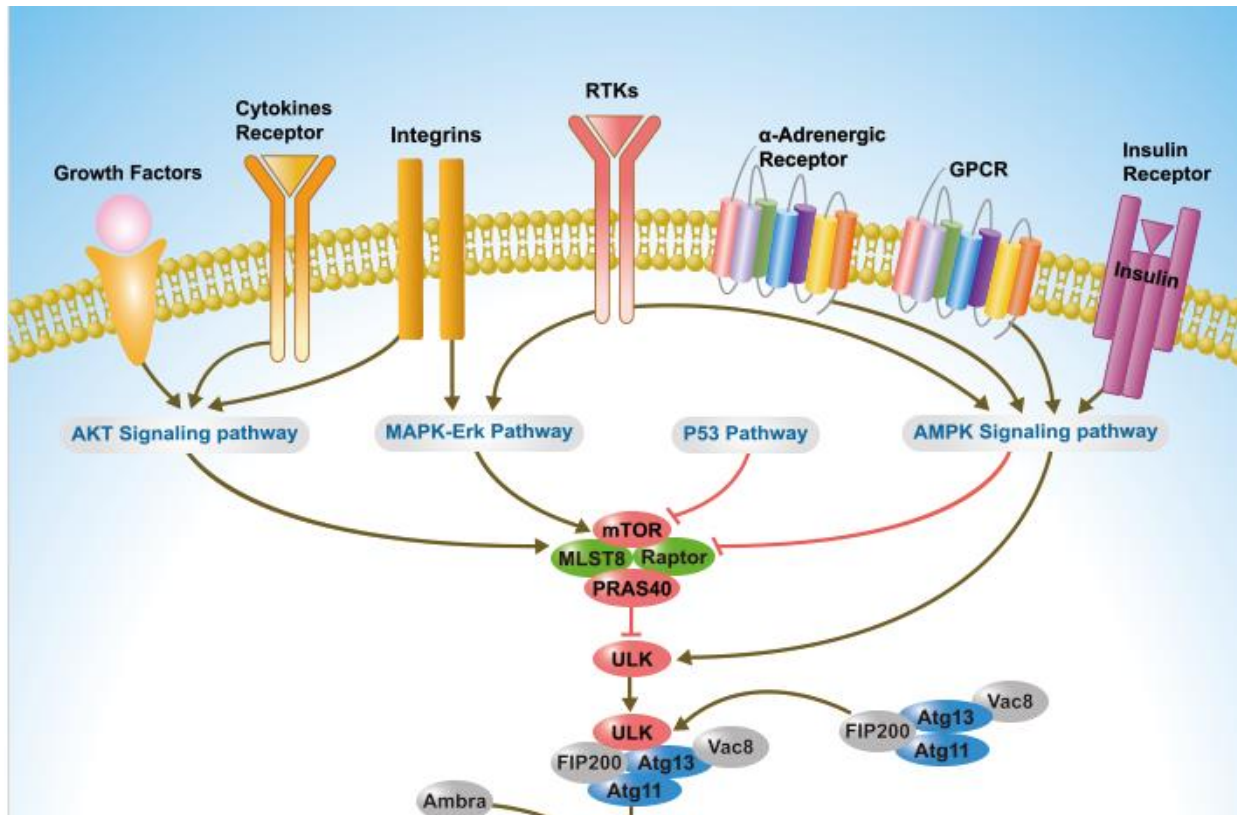
TRIM28 is essential for Autophagy initiation



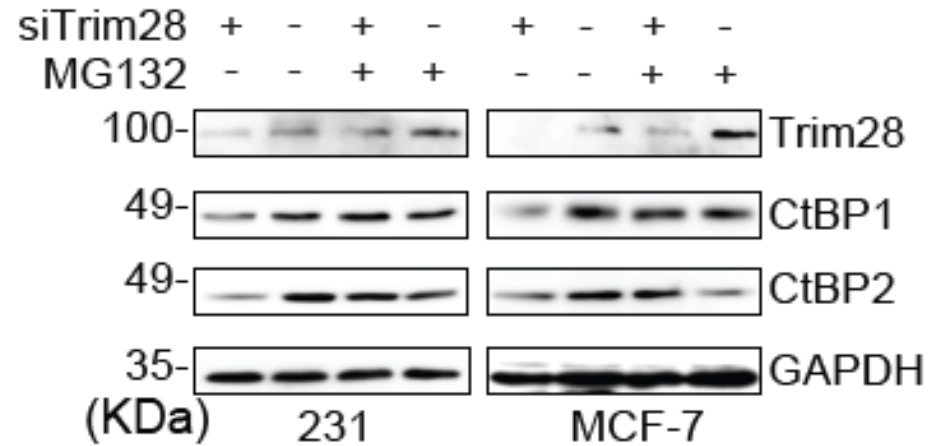
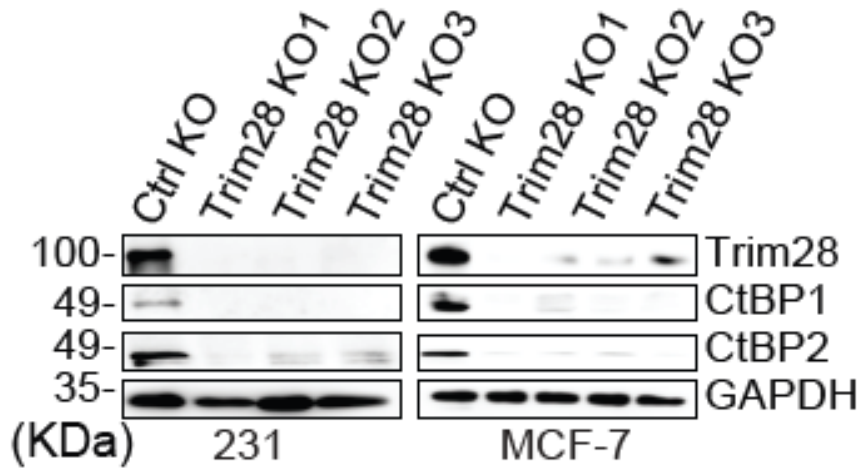
CtBP is a regulator of autophagy



AKT-mTOR-ULK1 axis is the regulatory target of CtBP

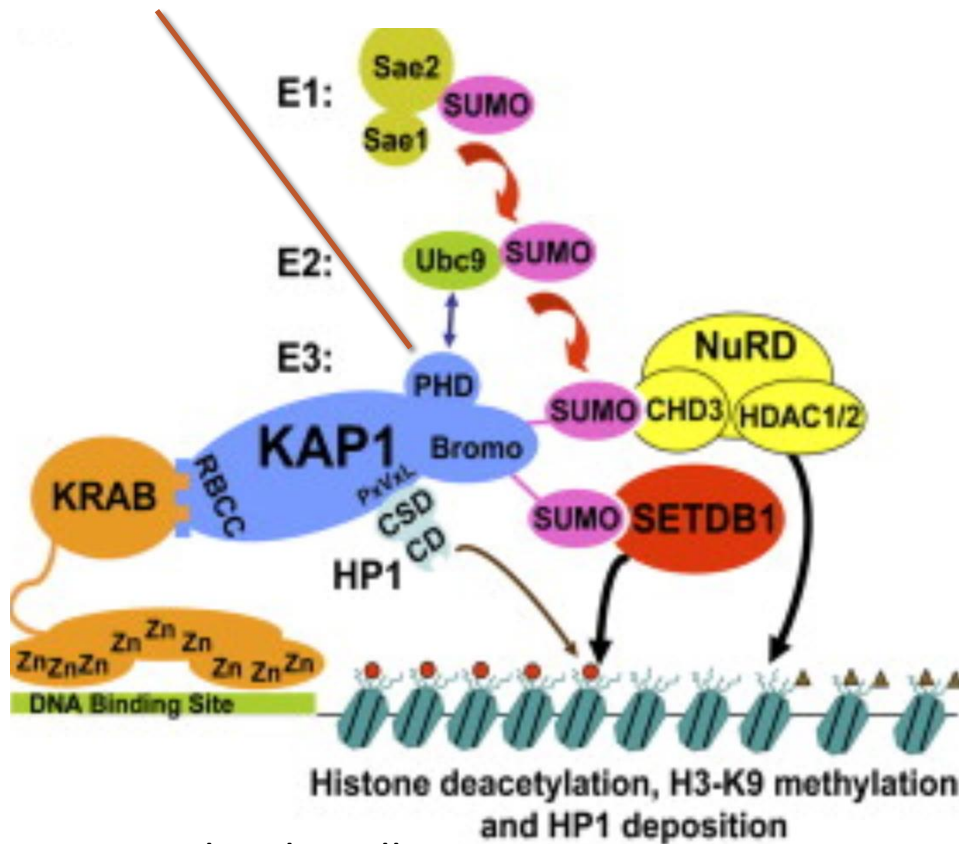


TRIM28 protect CTBP: mutual protection

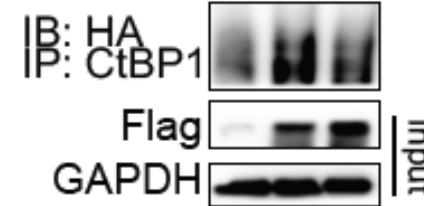


How Trim28 protects CtBP

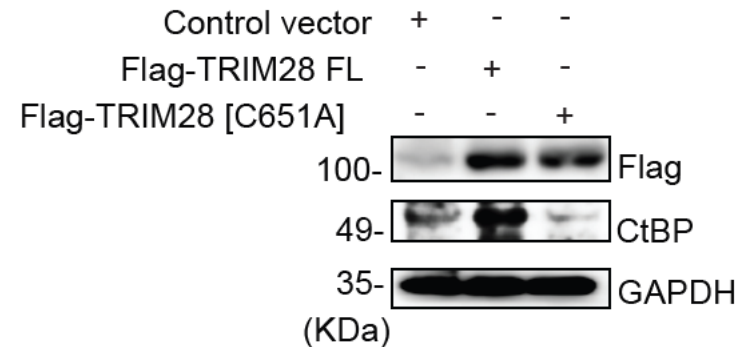
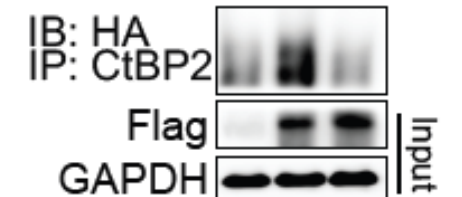
Cystein 651



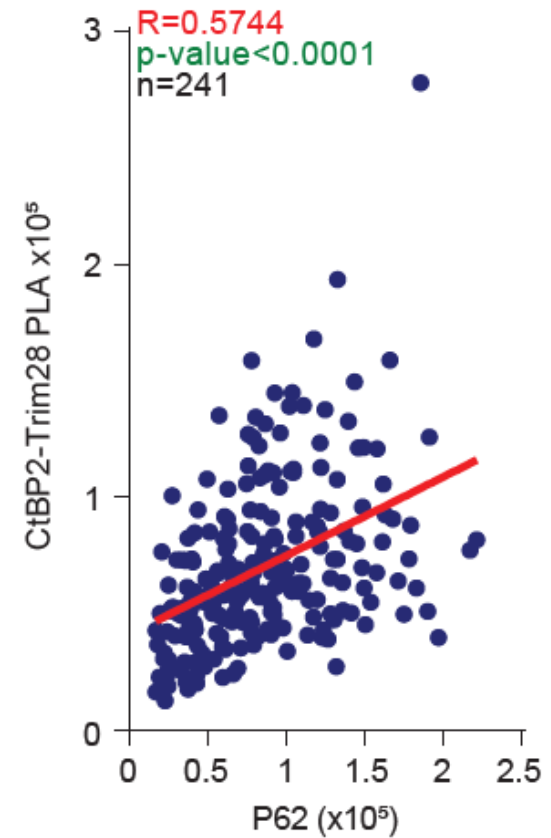
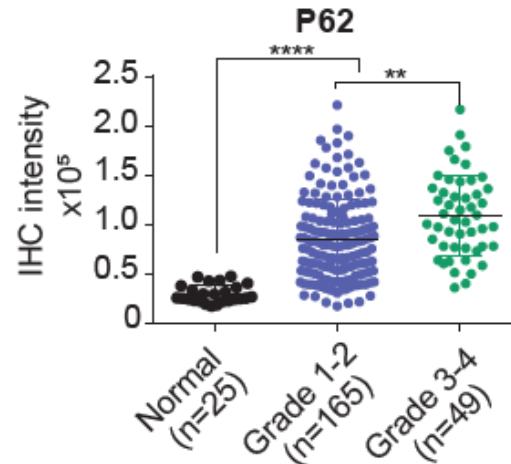
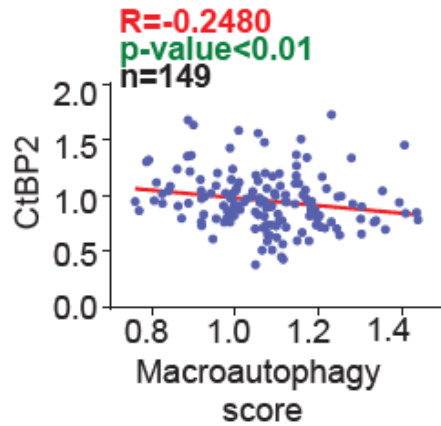
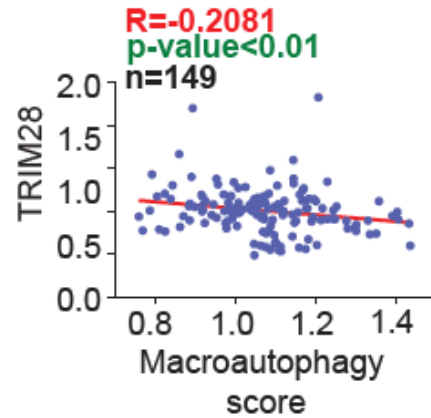
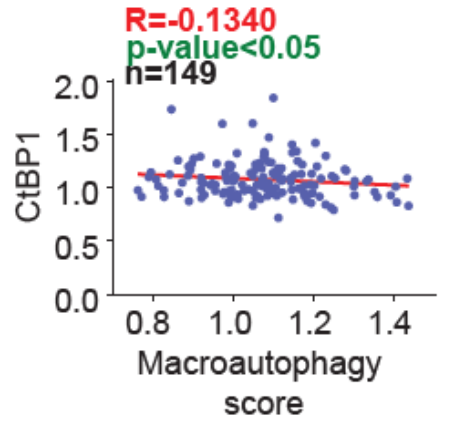
CtBP1	+	+	+
HA-SUMO1	+	+	+
Control	+	-	-
Flag-TRIM28 FL	-	+	-
Flag-TRIM28[C651A]	-	-	+



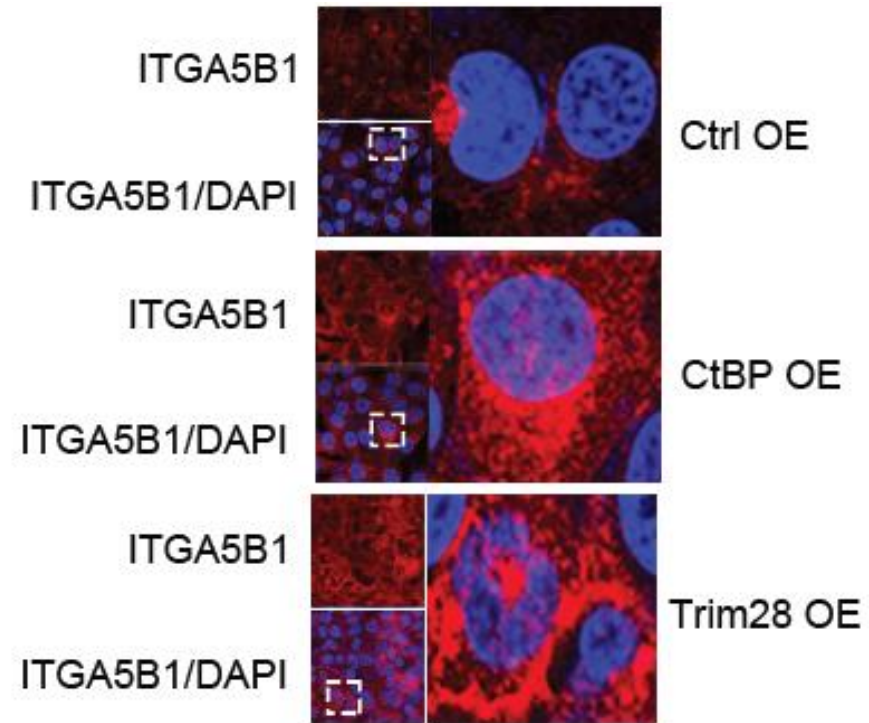
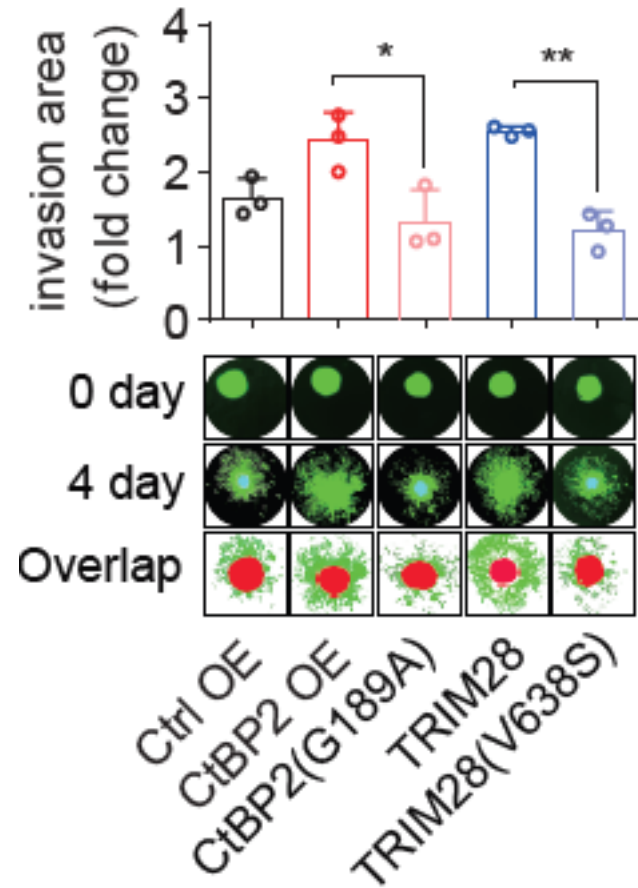
CtBP2	+	+	+
HA-SUMO1	+	+	+
Control	+	-	-
Flag-TRIM28 FL	-	+	-
Flag-TRIM28[C651A]	-	-	+



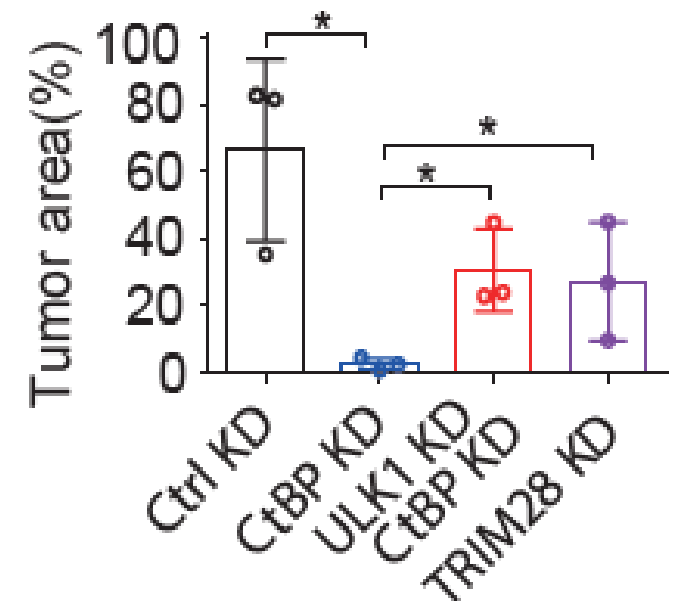
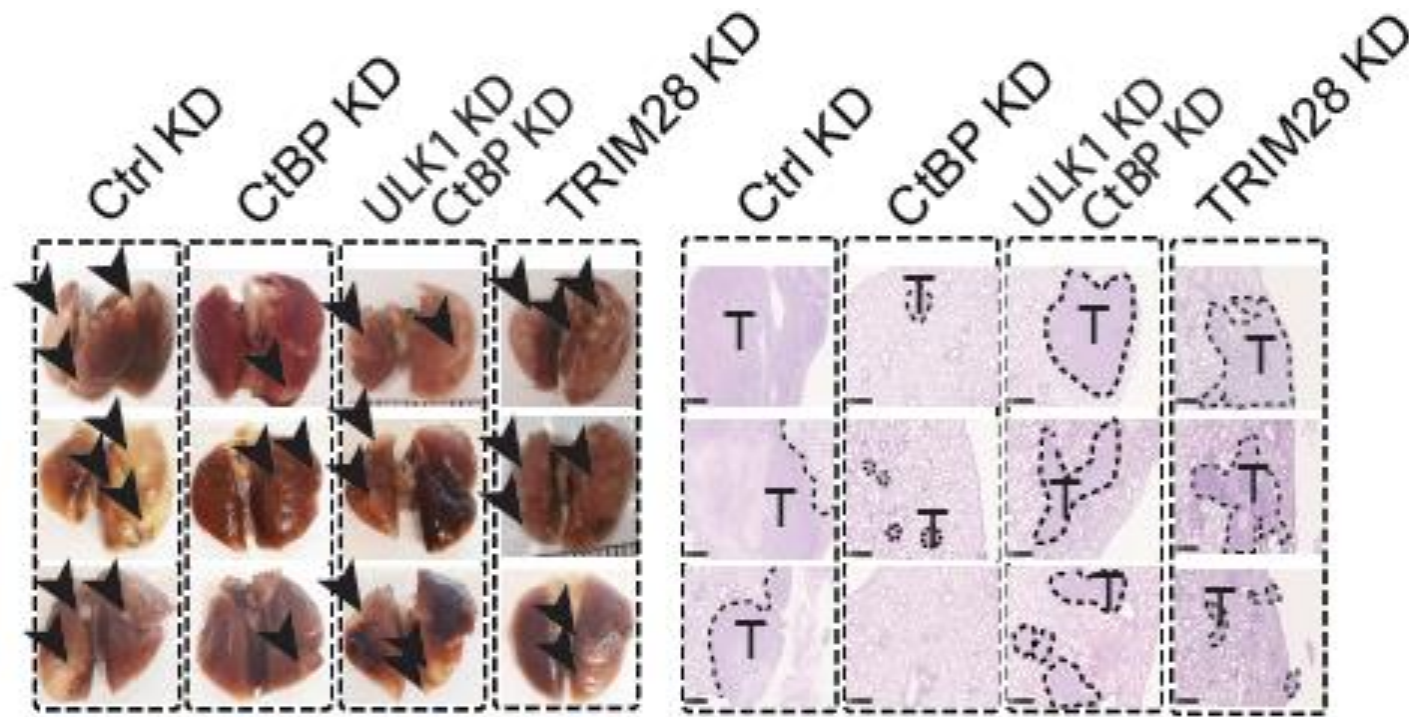
CtBP/TRIM28 complex represses autophagy to “promote” metastasis

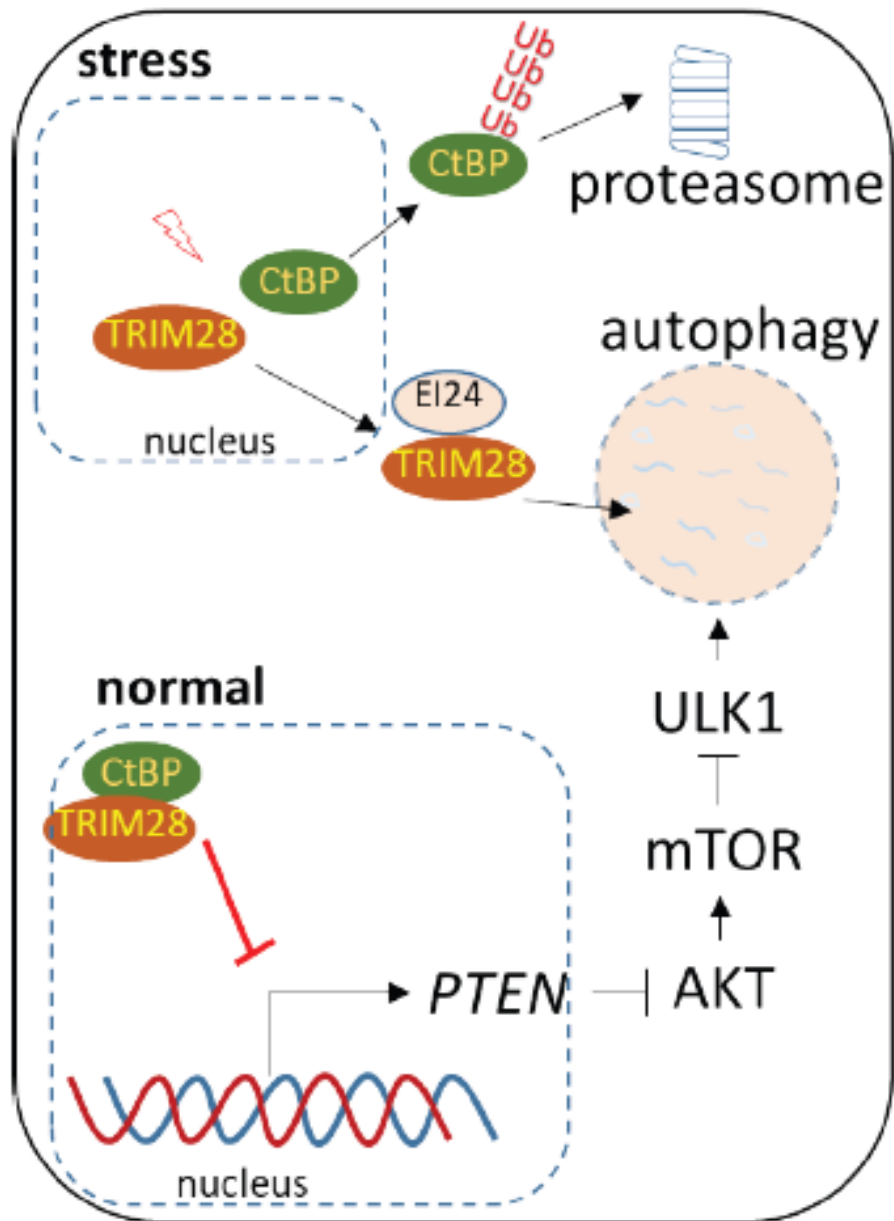


Integrin is a potential target of autophagy



CtBP/TRIM28 complex represses autophagy to “promote” metastasis





Conclusions

- CTBP and TRIM28 forms complex
- CTBP and TRIM28 protect each other
- CTBP and TRIM28 repress autophagy
- CTBP and TRIM28 promote cancer metastasis

Autophagy in metastasis

ULK1 phosphorylates Exo70 to suppress breast cancer metastasis(NC Mao, Zhan et al. 2020)

Autophagy inhibition elicits emergence from metastatic dormancy by inducing and stabilizing Pfkfb3 expression(NC La Belle Flynn, Calhoun et al. 2019)

RIPK1-mediated induction of mitophagy compromises the viability of extracellular-matrix-detached cells(NCB Hawk, Gorsuch et al. 2018)

Autophagy promotes the survival of dormant breast cancer cells and metastatic tumour recurrence(NC Vera-Ramirez, Vodnala et al. 2018)

HIF-1 α promotes autophagic proteolysis of Dicer and enhances tumor metastasis (JCI Lai, Li et al. 2018)

Survival of cancer cells is maintained by EGFR independent of its kinase activity(Cancer cell, Weihua, Tsan et al. 2008)

Bi-facial function of autophagy in metastasis



Pro-Metastasis



Protect premetastatic cells from stresses

Protect the detached cells from anoikis

Inducing the detached cells entering dormancy

Protect the circulating tumor cells (CSC)



Survive

Anti-metastasis



Reducing the infiltration of immune cells in primary tumor

Inducing cancer cell apoptosis

Inducing anti-cancer immunology

Inducing mitophagy



Death

Thank you

Current Lab Members

Tai Lixin
Wang Lifen
Tang ping
Zhu Dongliang
Li jiajia
Xu hongxia
Liu Tianyu
Li Junyi

Past members

Li Jingjing
Li Peipei
keng ieng Wong
Zhao Zhiqiang
Zhang Chao
Hao Dapeng

Collaborators

Macau U, FHS, Chuxia Deng, Han-ming Shen, Kai Miao et al.

Xiamen U, Lin Shuhai

Columbia U, Kevin Gardner

FHS core facilities:
Animal facility, imaging core, metabolomics core etc.

Funding source: UM-MYRG, Macau-FDCT and NSFC