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OMICS International has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.



Epigenetic regulation of breast cancer metastasis by miR-106b-BRMS1L-FZD10 signaling.

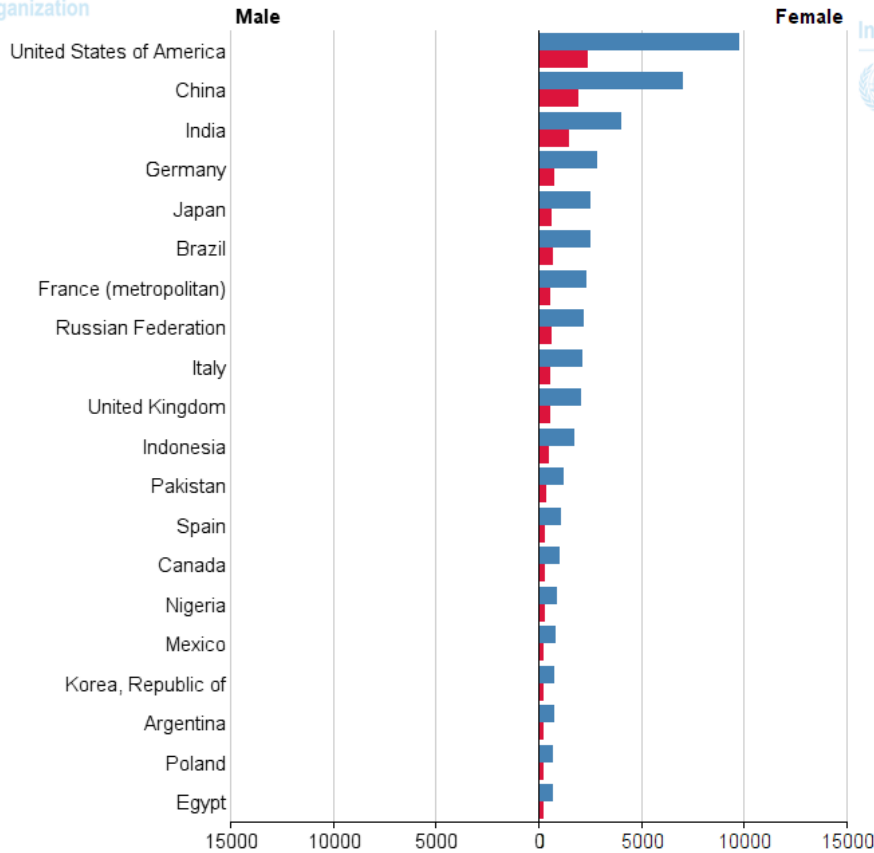
Breast Tumor Center, Sun Yat-sen Memorial Hospital,
Sun Yat-sen University, China

Chang Gong

Apr.27 2015

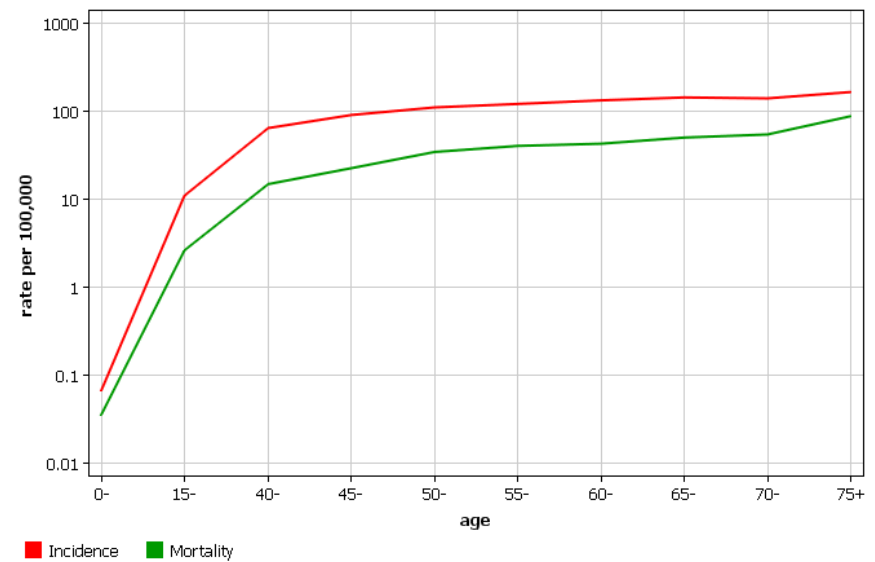
Metastasis is responsible for around 90% of breast cancer-associated mortality.

International Agency for Research on Cancer Breast, adults



World

Breast cancer

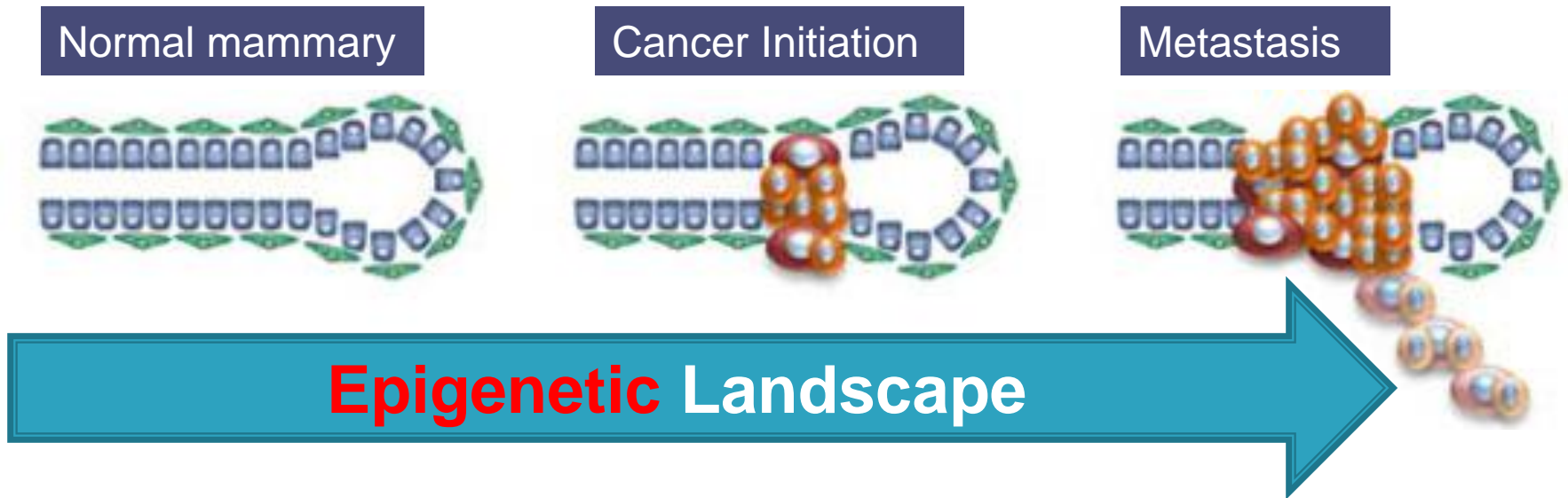


GLOBOCAN 2008 (IARC) - 13.3.2013

GLOBOCAN 2012 (IARC) (11.2.2014)

5-year prevalence
Incidence

Epigenetic repression of metastasis-associated genes has a significant role in suppressing metastasis.



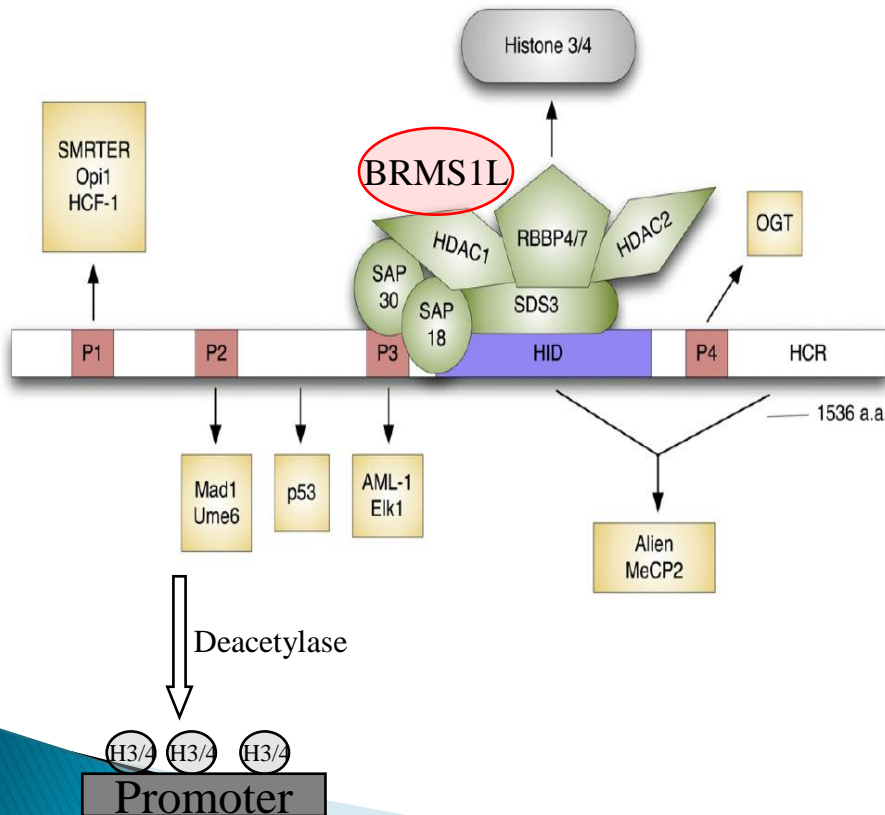
- DNA methylation and chromatin remodeling
- **Variant histones H2A : HDAC repressor complex**
- **MicroRNAs**

SIN3–HDAC complex are important inhibitors in epigenetic silencing of target genes.

core switch-independent 3 (SIN3)–HDAC

BRMS1L

(Breast cancer metastatic suppressor 1-like)



Molecular weight: 40KD

A co-suppressor of mSin3A /HDAC complex

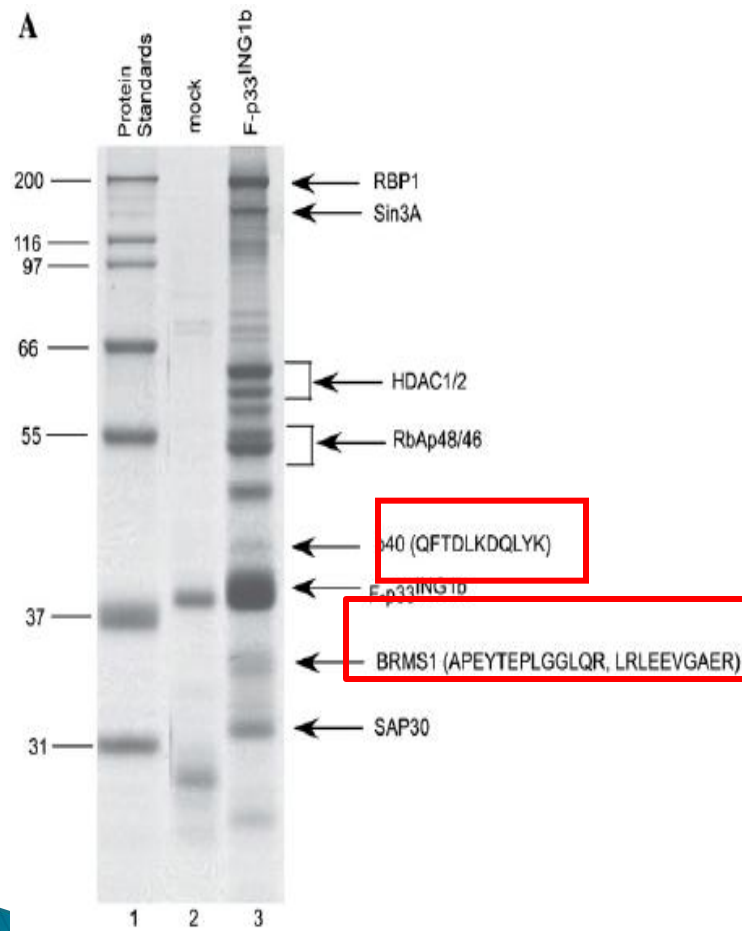
Strong histone deacetylase (HDAC) activity

Its biology function is unknown.

AnatolyY. Nikolaev , et al , 2004

Transcription suppressor

BRMS1-Like (BRMS1L) is highly homologous to BRMS1 .



- 57% identity and 79% similarity
- BRMS1 suppresses metastasis of multiple types of malignancies.
- BRMS1 gene is often deleted or epigenetically silenced in breast cancer.

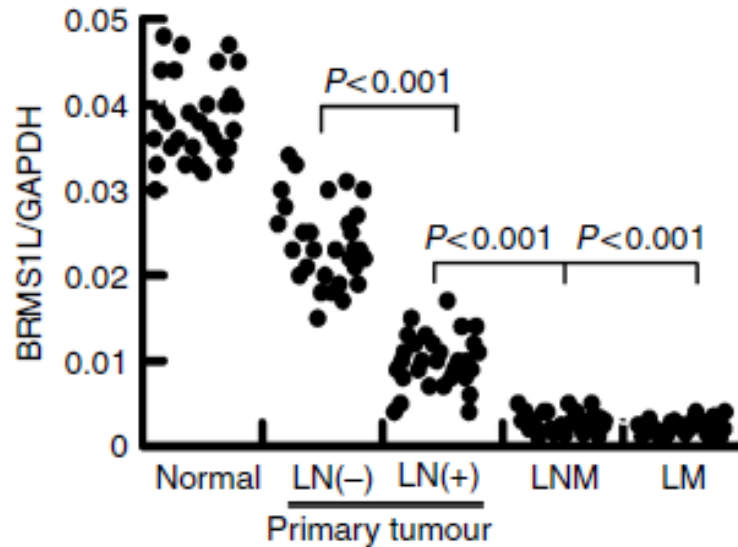
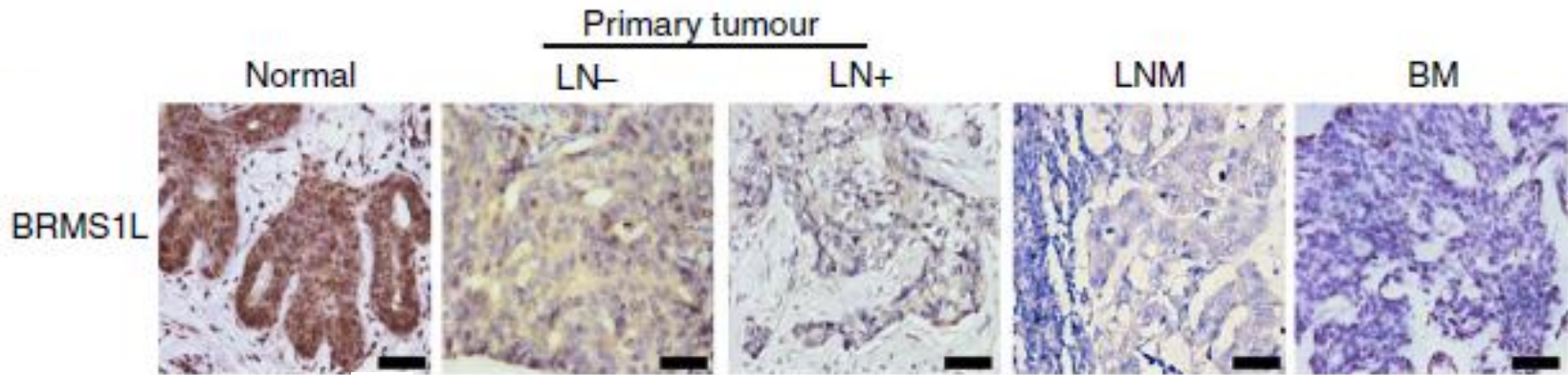
Cicek M, et al , BBRC,2004, 323:1216-1222.

Questions

Whether BRMS1L plays a functional role in suppressing breast cancer metastasis?

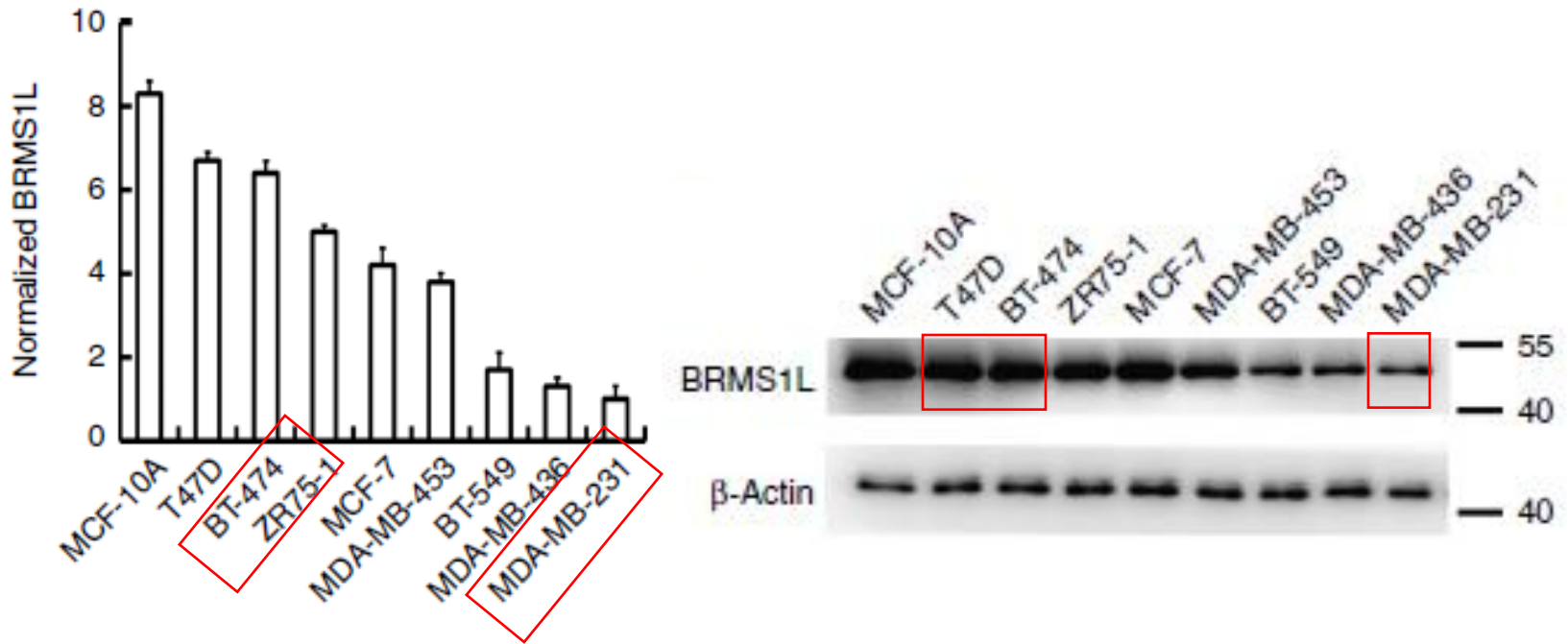
What is the mechanism of BRMS1L(BRL) in breast cancer cells?

BRMS1L expression is much lower in breast cancer tissues.



- LN+: positive lymph node
- LN-: negative lymph node
- LNM: lymph node metastasis
- BM: brain metastasis
- LM: liver metastasis

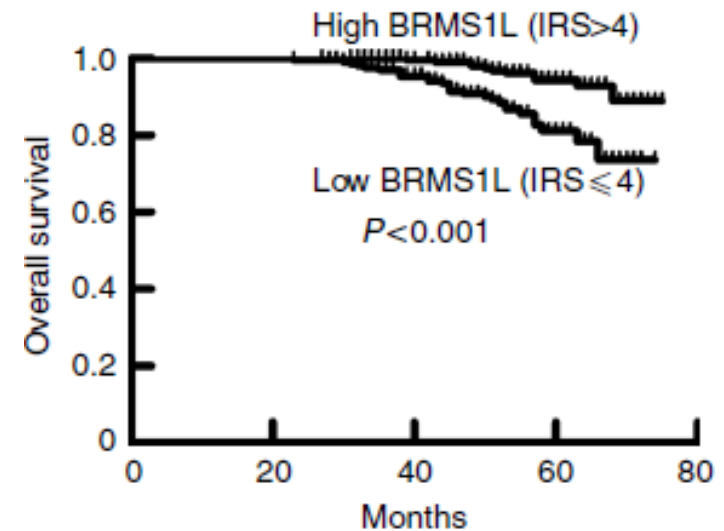
The mRNA and protein level of BRMS1L was much lower in mesenchymal-like breast cells.



Breast cancer patients with high BRMS1L had low metastatic potential and a longer survival.

BRMS1L	IRS>4	IRS≤4	P value
Age(years)			0.108
≤45	96	106	
>45	125	101	
Size(cm)			0.005
≤2	115	80	
>2	106	127	
Histological grade			0.109
I	79	56	
II	95	94	
III	47	57	
Stage			0.021
I	79	49	
II	108	116	
III-IV	34	42	
Positive Lymph node			<0.001
≤3	185	126	
>3	36	81	
ER			0.287
positive	166	146	
negative	55	61	
HER2			0.238
negative	179	158	
positive	42	49	
Metastasis			<0.001
no	197	153	
yes	24	54	

N=428



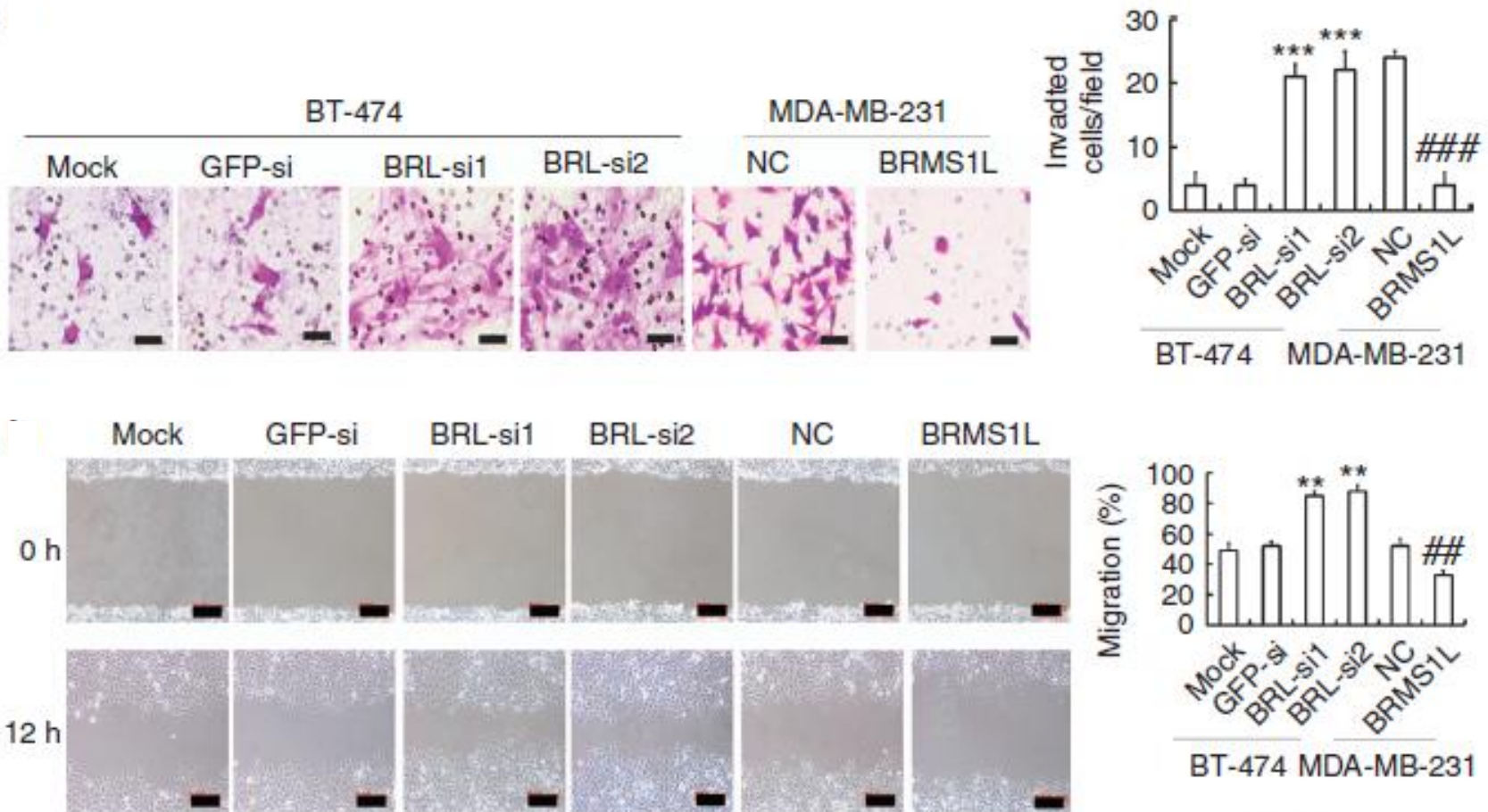
Median follow-up: 55m



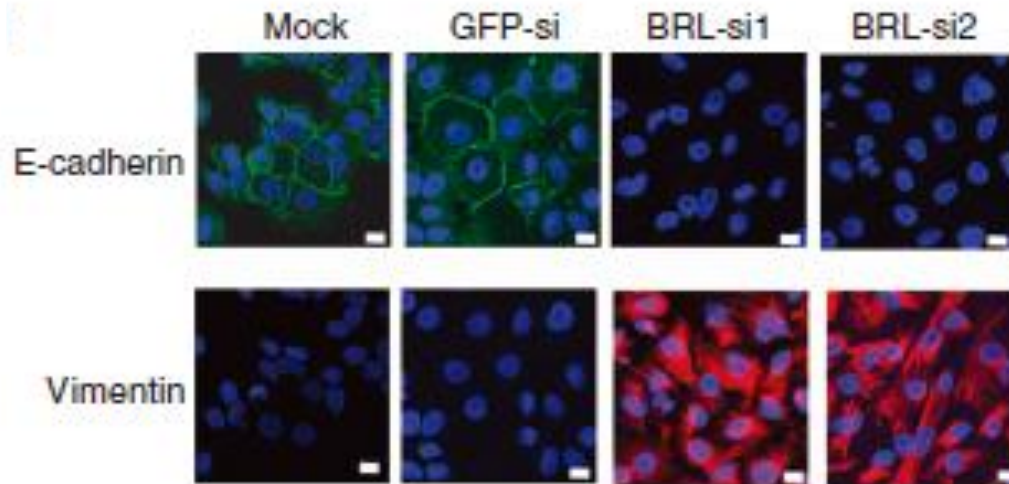
**Reduced BRL expression is associated
With breast cancer metastasis.**

**Whether BRMS1L exerts a metastatic
suppressing function in breast cancer cells?**

BRMS1L suppresses migration and invasion of breast cancer cells.



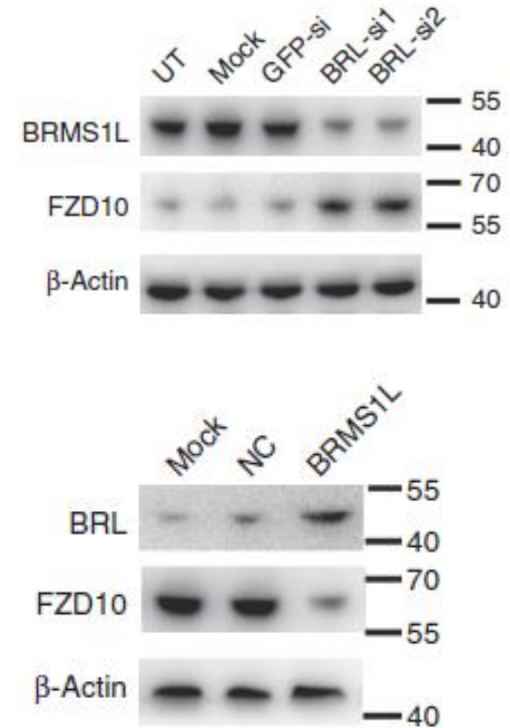
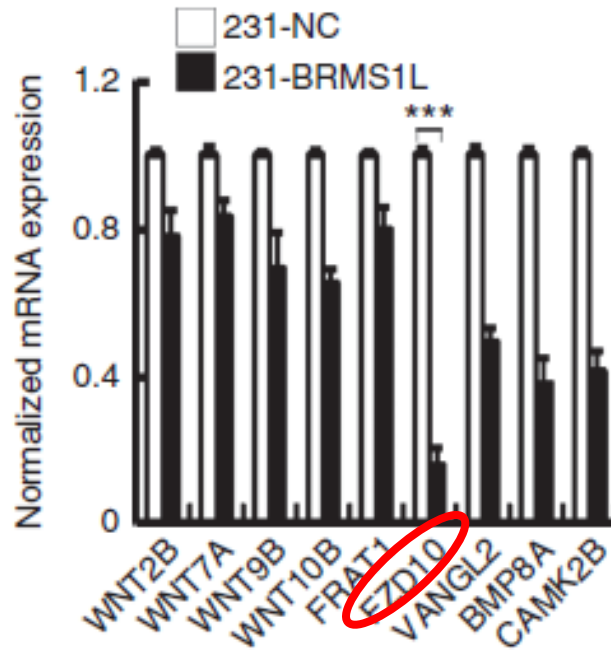
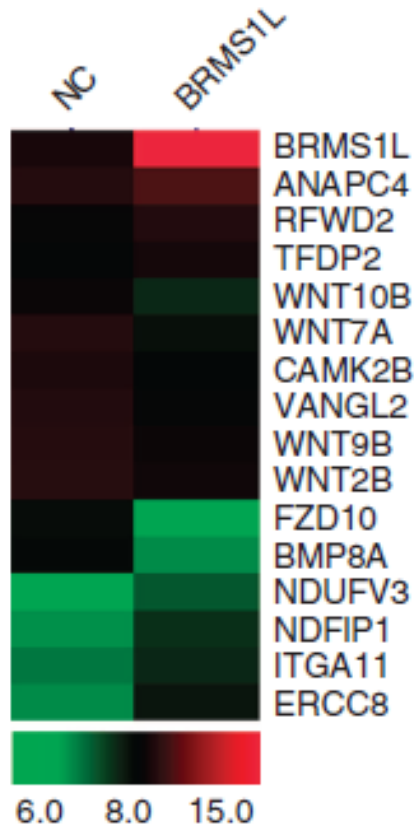
BRMS1L inhibits epithelial-mesenchymal transition (EMT).





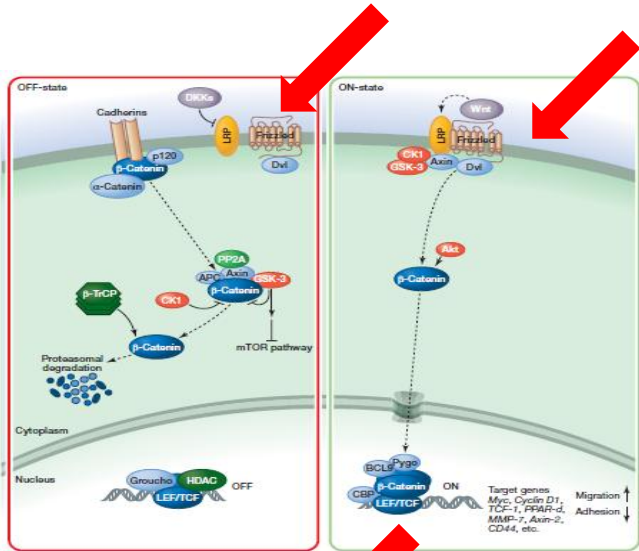
BRMS1L inhibits the migration and invasion of breast cancer cells by suppressing EMT.

BRMS1L suppresses FZD10 expression



FZD10: Frizzled10

FZD10 promotes tumor cell growth and metastasis by activation of Wnt pathway.



- codes for a seven-transmembrane-receptor of wnt signaling pathway

BBRC 1999.

- Highly expressed in cervical cancer ,colon cancer , gastric cancer and synovial sarcoma

Tumor cell growth, metastasis

Oncogene 2005

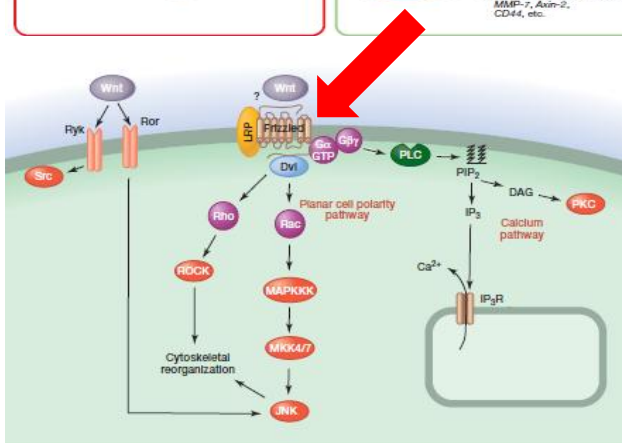


Figure 2. Non-canonical Wnt signaling pathways.

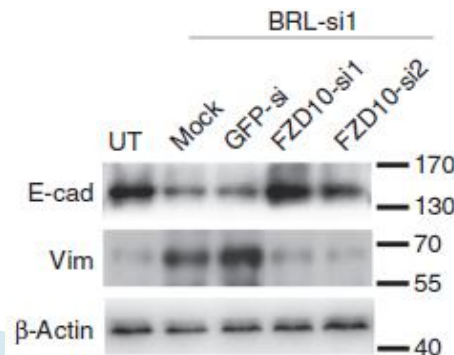
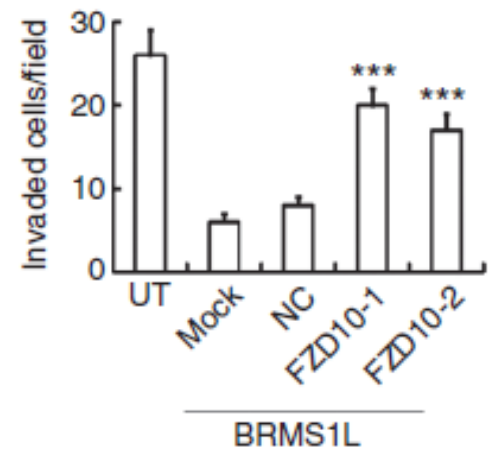
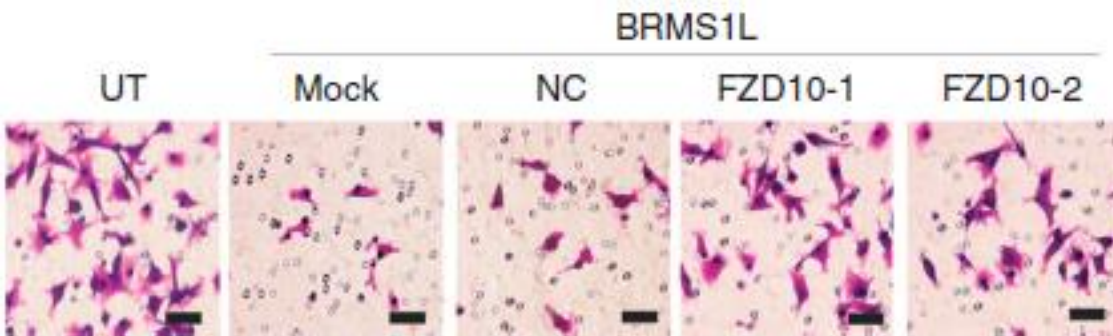
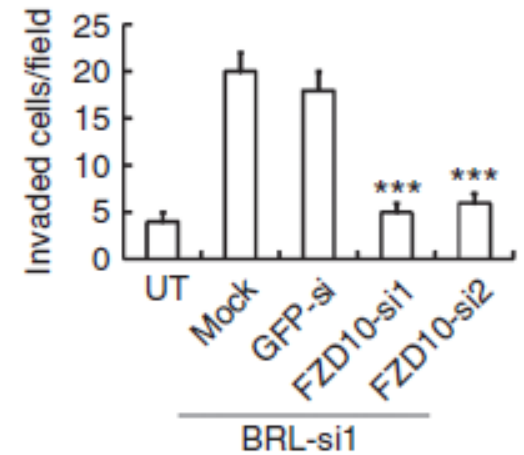
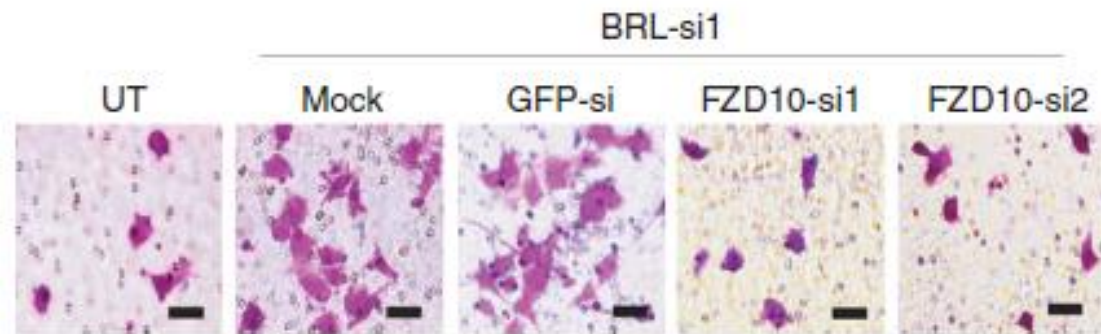
- Positive regulator of canonical wnt-β-catenin-TCF signaling pathway

Int J Mol Med (2002)

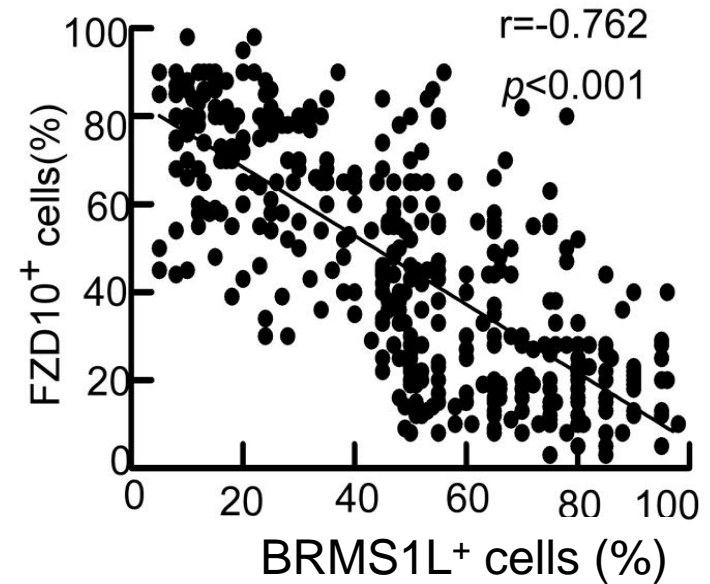
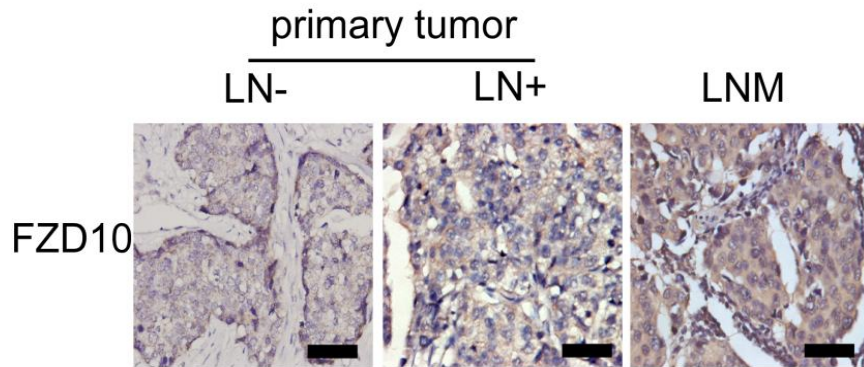
- Activate non-canonical Dvl-Rac1-JNK pathway

Oncogene 2009

BRMS1L inhibits breast cancer cell invasion and EMT via suppressing FZD10 expression.



FZD10 expression is inversely correlated with BRMS1L in breast cancer samples.

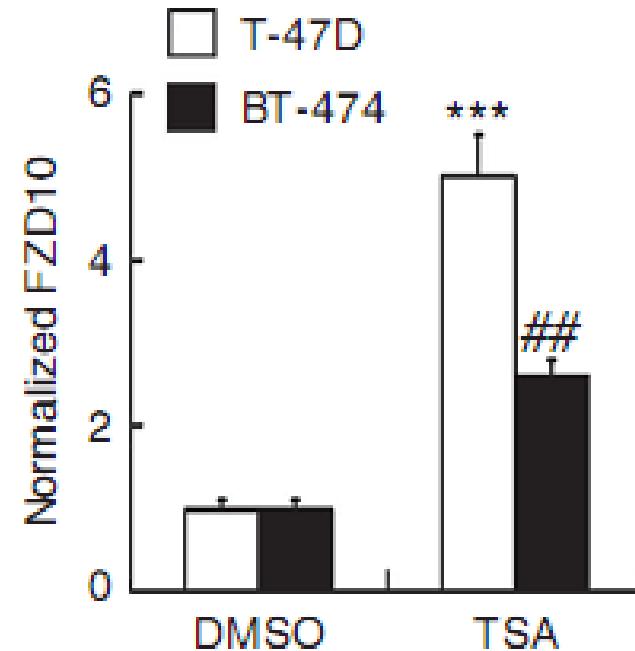
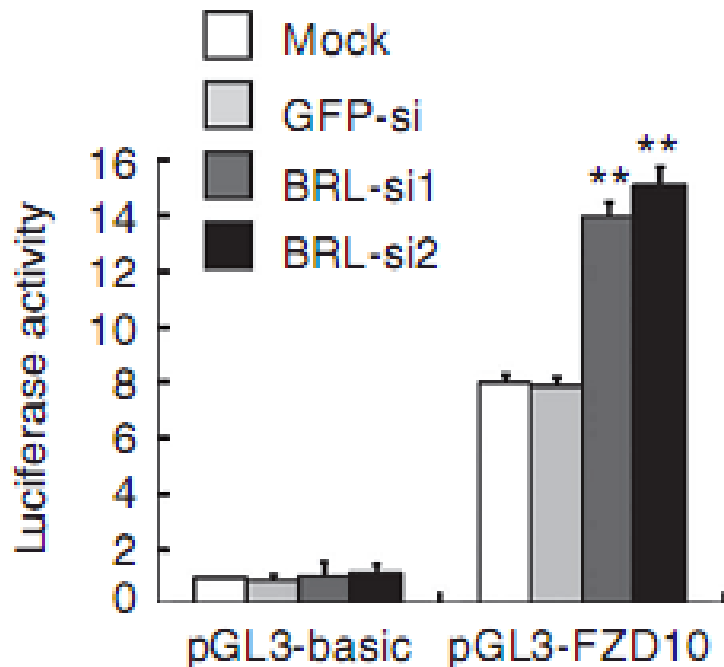




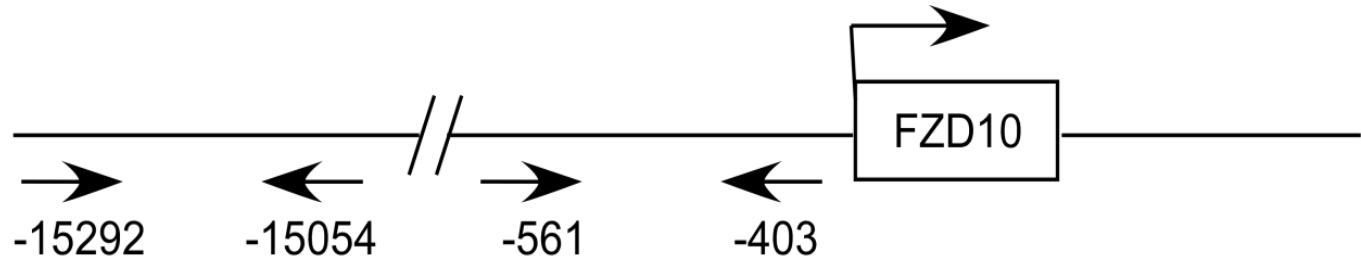
BRMS1L inhibits EMT and invasion of breast cancer cells via downregulating fzd10.

BRMS1L regulates fzd10 promoter activity by histone deacetylation.

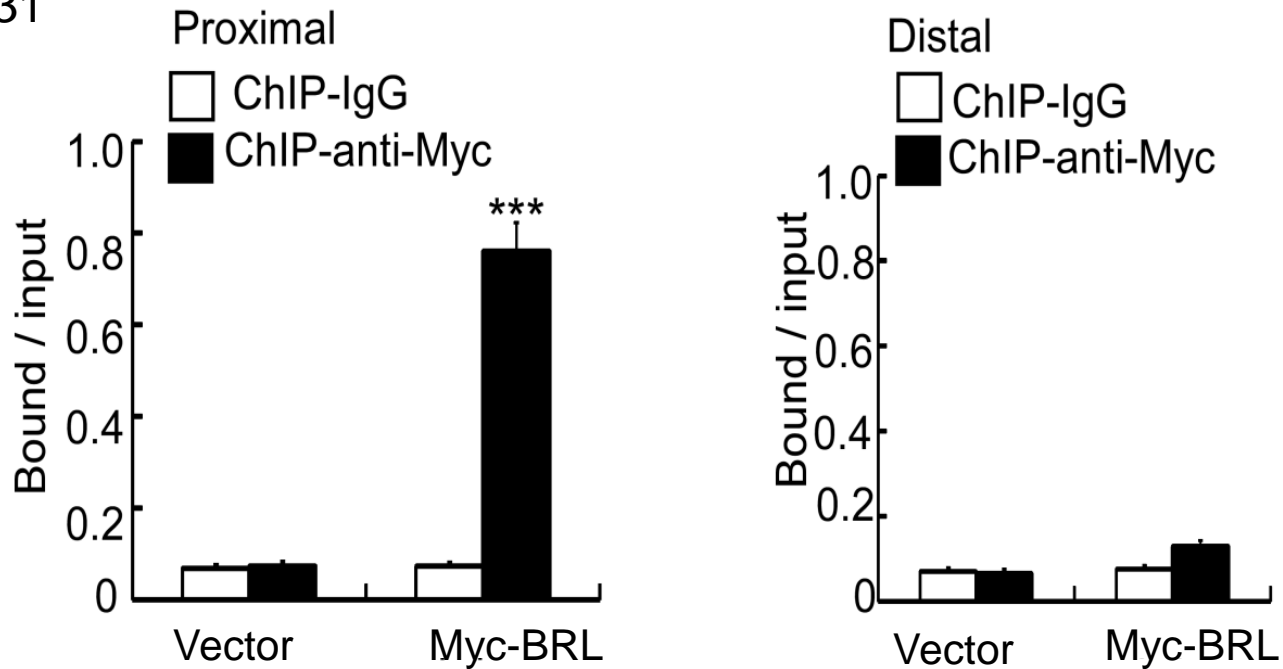
T47D



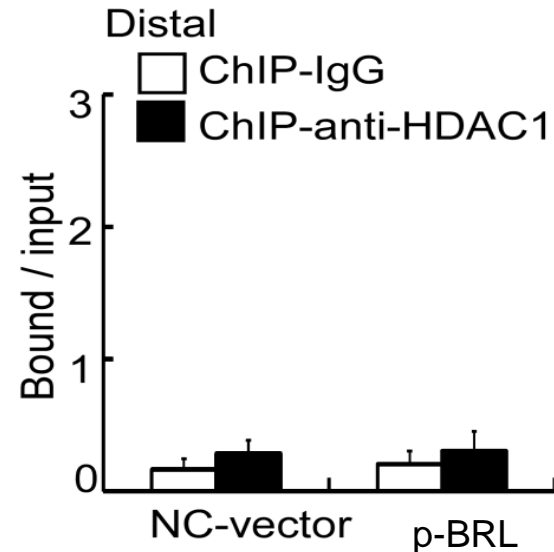
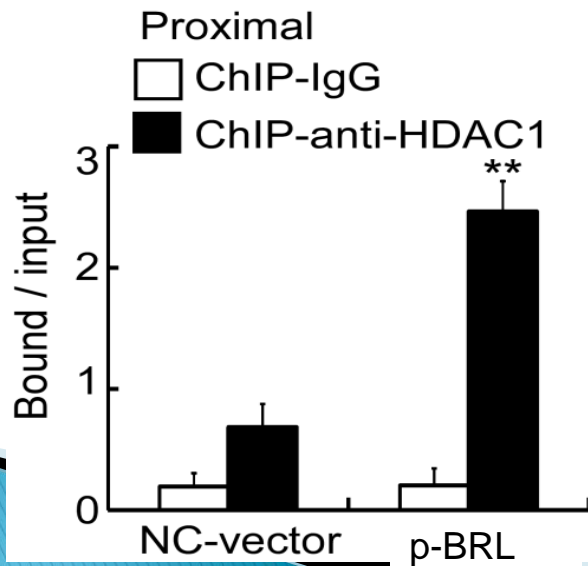
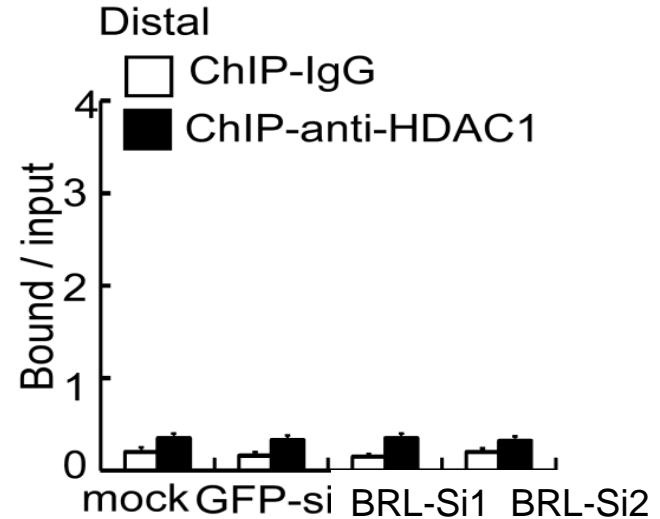
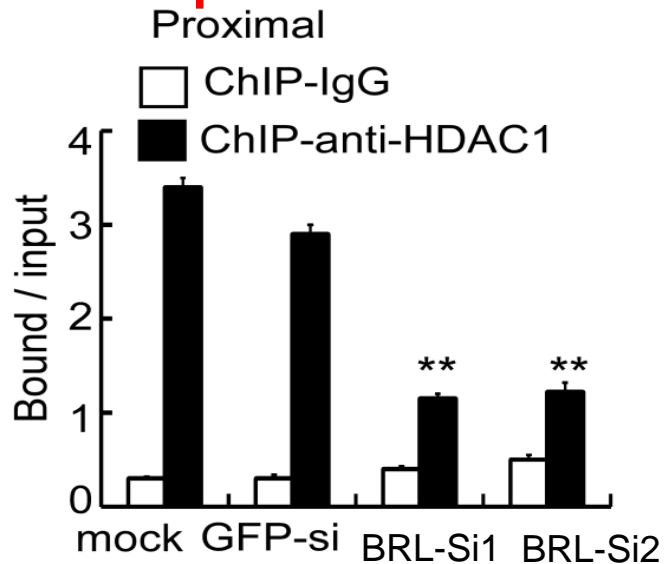
BRMS1L binds to the *fzd10* promoter



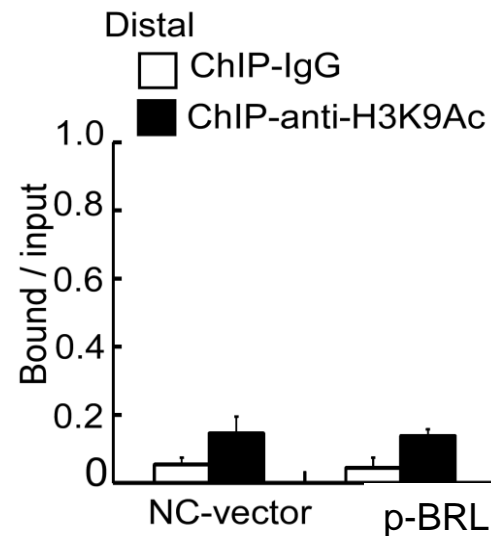
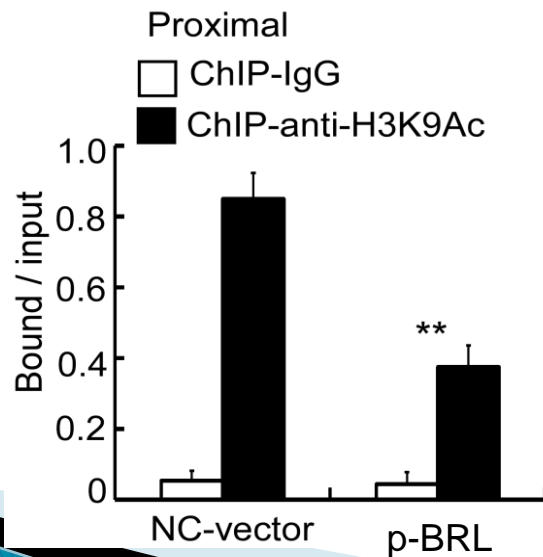
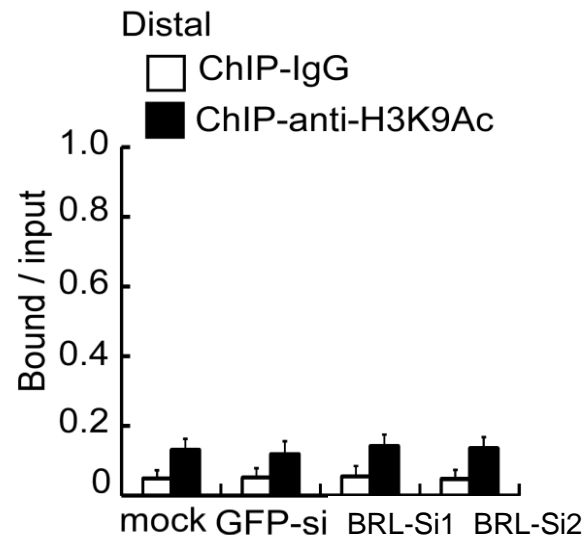
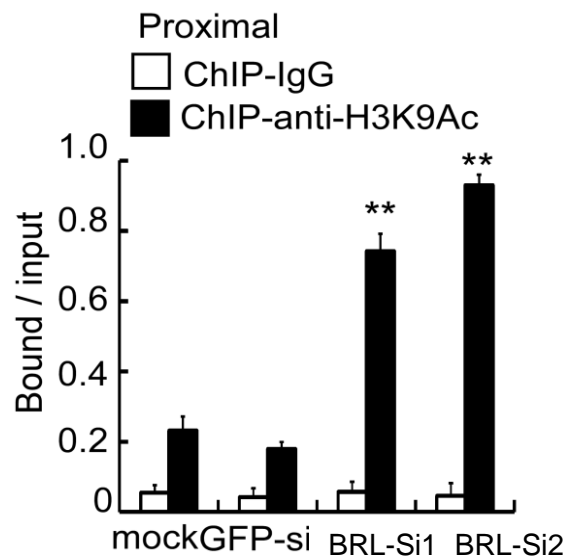
MDA-MB-231



BRMS1L increases recruitment of HDAC1 to the *fzd10* promoter.



BRMS1L suppresses the binding of HDAC1 substrates to *fzd10* promoter



H3K9Ac:
a substrate of HDAC
deacetylase

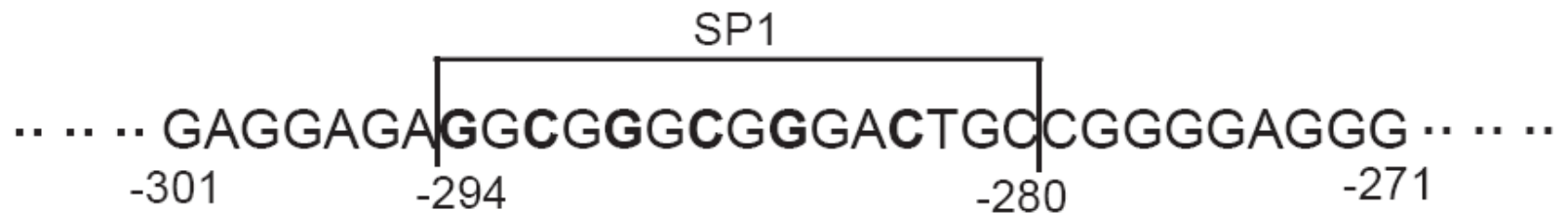
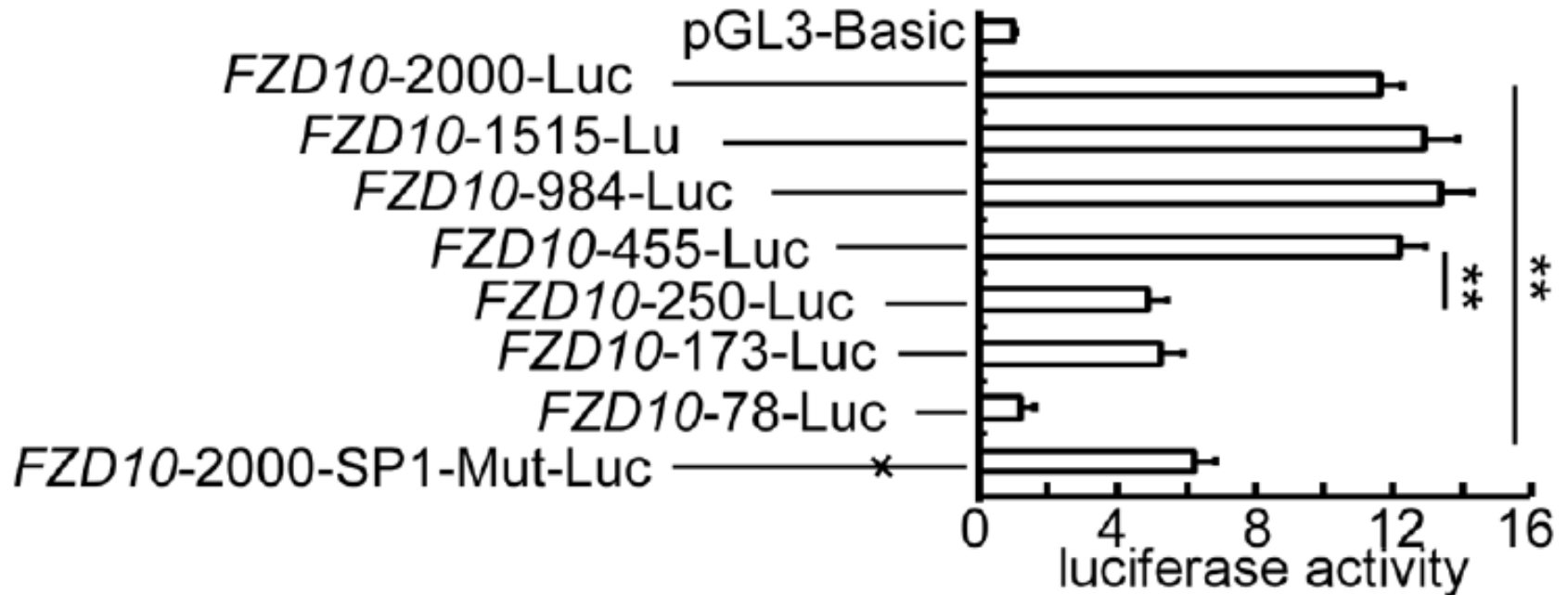


BRMS1L increases the recruitment of HDAC1/2 complex to *fzd10* promoter and thus reducing acetylation of HDAC1/2 substrates.

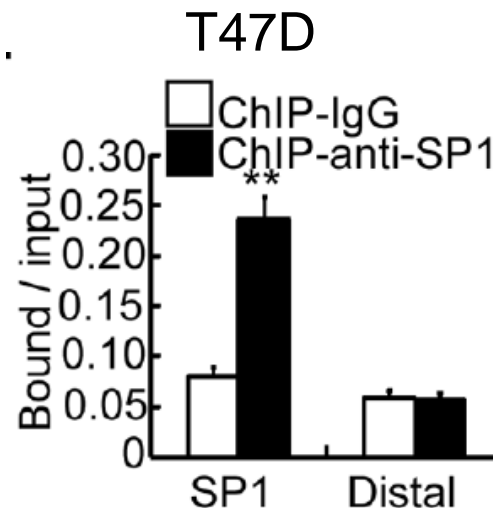
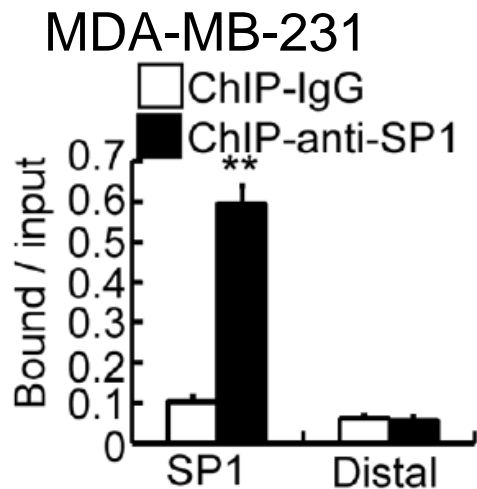
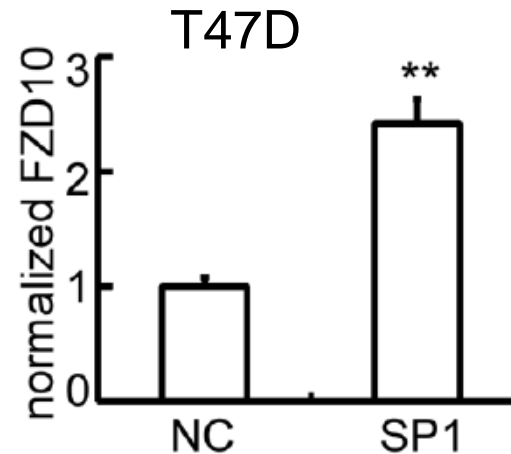
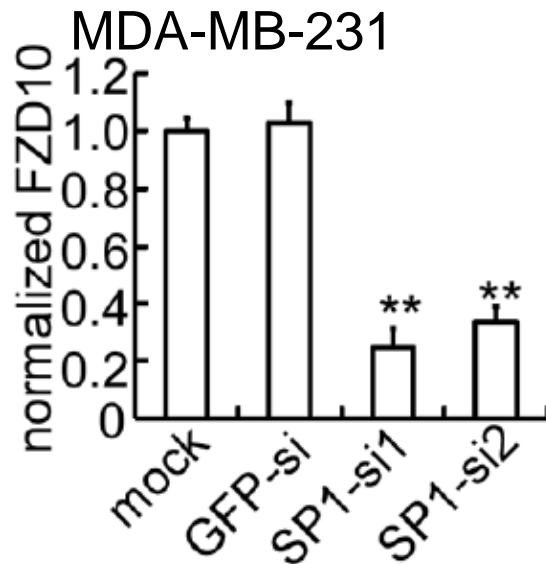


**What activates the transcription
of *fzd10*?**

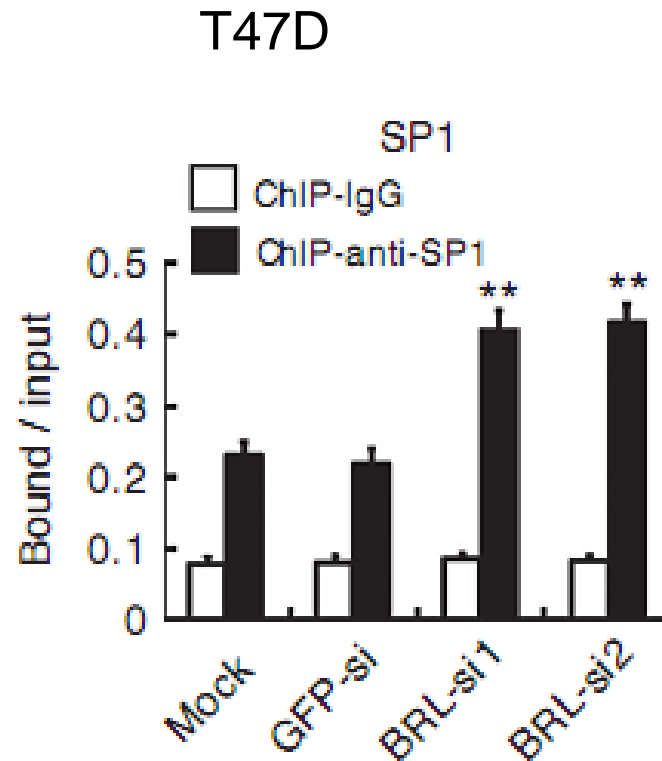
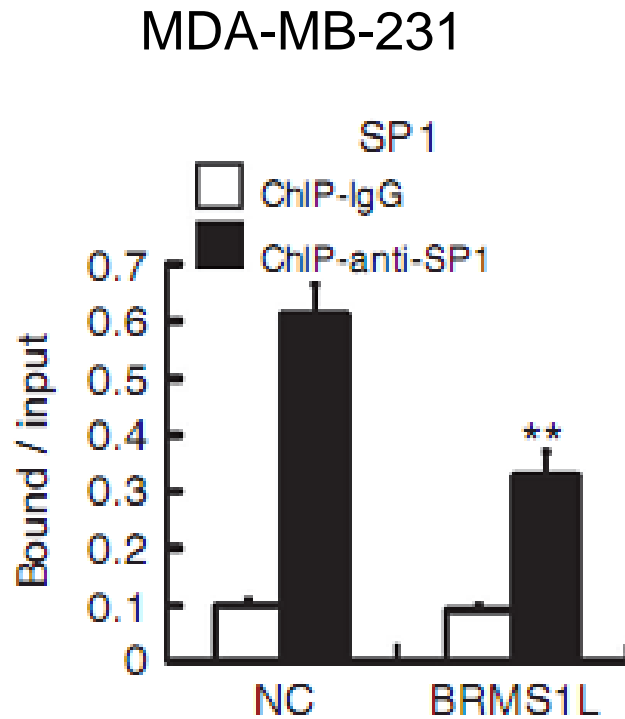
An SP1-binding site was involved in the full trans-activation activity in the FZD10 promoter region.



SP1-mediated transcription is responsible for FZD10 upregulation in breast cancer cells.



BRMS1L suppresses the binding of SP1 to *fzd10* promoter



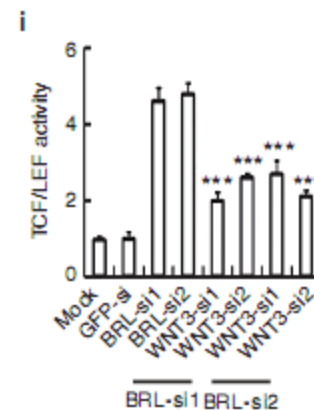
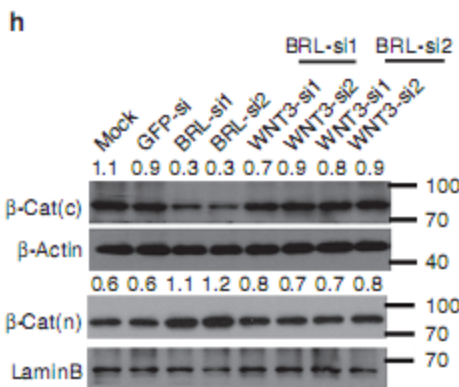
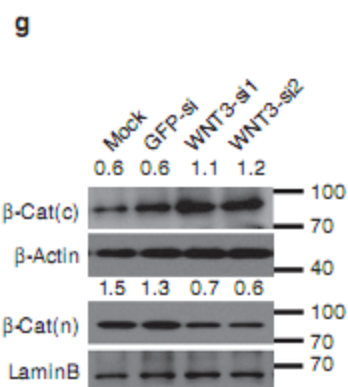
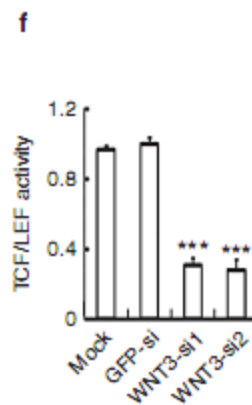
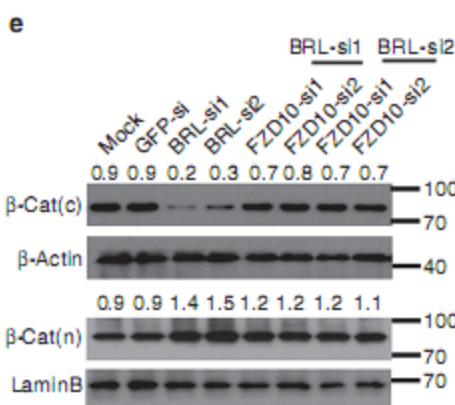
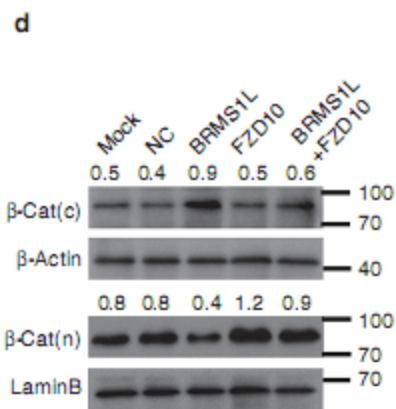
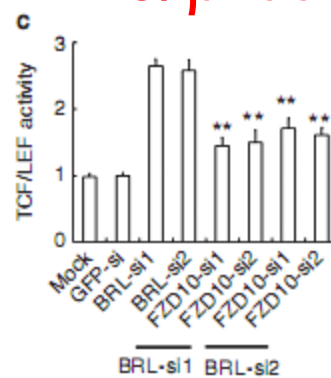
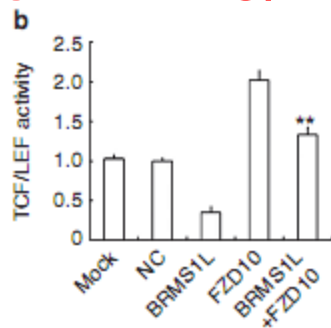
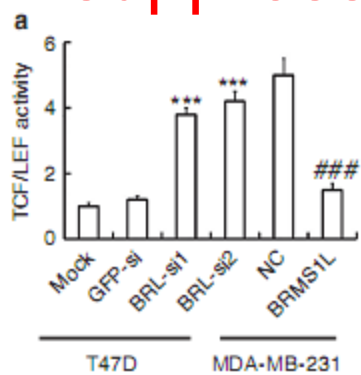


BRMS1L attenuates SP1-mediated FZD10 transcriptional activation probably by reducing histone acetylation at FZD10 promoter.



Whether BRMS1L regulates Wnt signaling pathway via FZD10?

BRMS1L suppresses WNT3/FZD10/ β -catenin pathway.

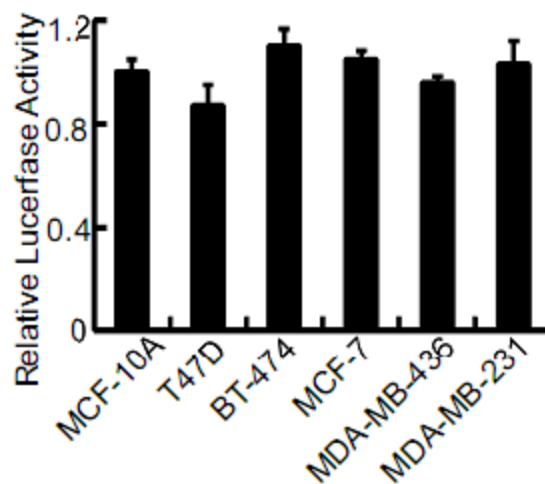




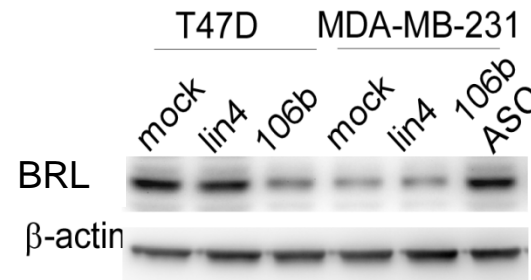
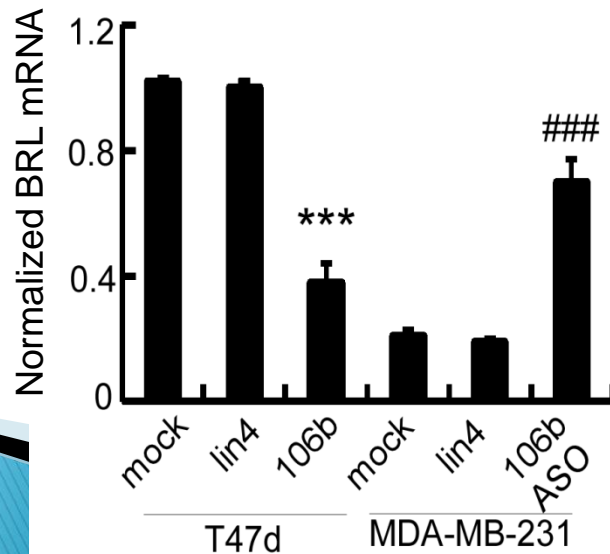
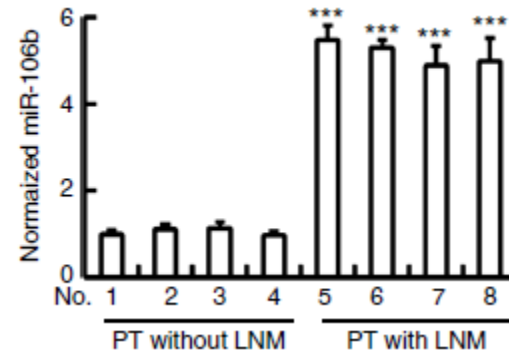
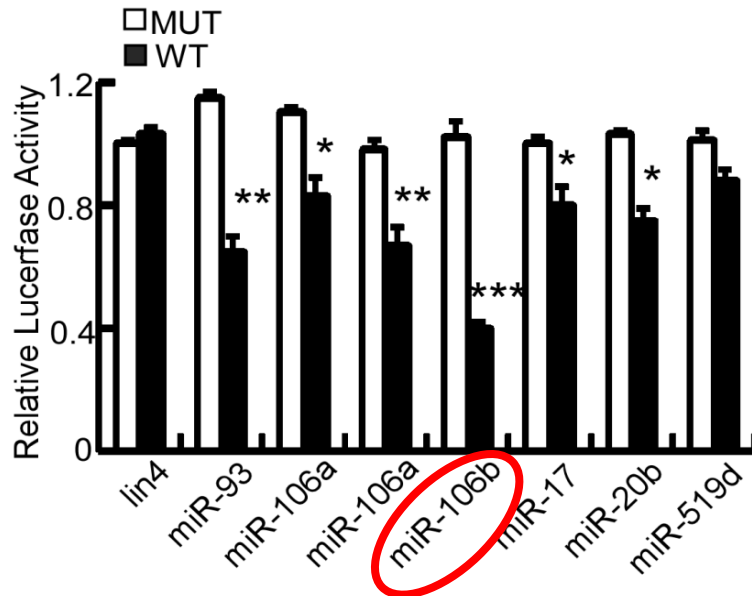
Why BRMS1L is differentially expressed in breast cancers with different metastatic potential ?

Target scan predicts microRNAs targeting BRL-3'UTR

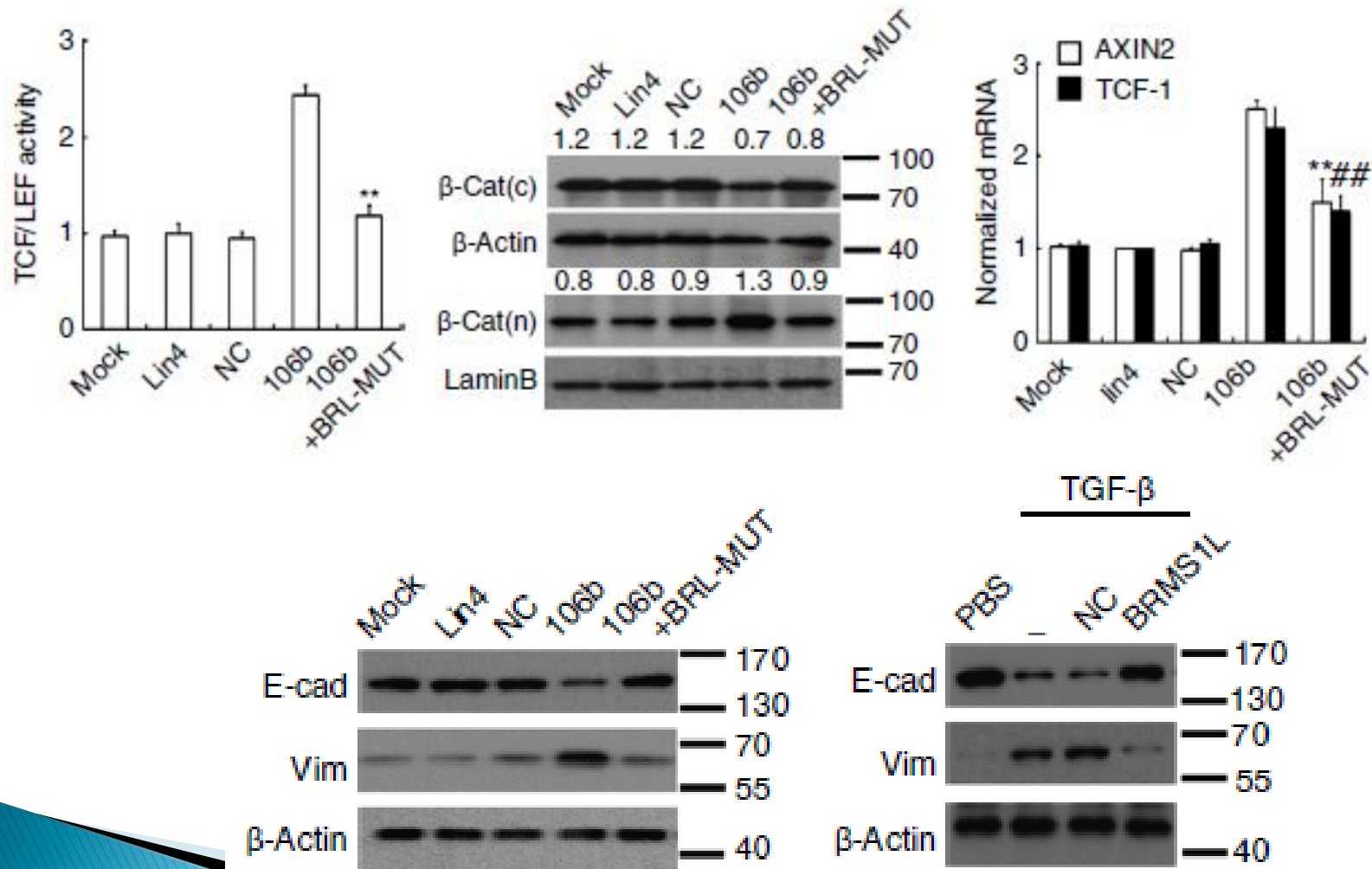
Preferential conservation	microRNAs
High probability	miR-93、 miR-20a、 miR-106a、 miR-106b、 miR-17、 miR-20b、 miR-519d (position 1128-1135 of p40 3' UTR) (position 576-582 of p40 3' UTR)
Lower probability	miR-520a/b/c/d/e、 miR-302a/b/c/d/e、 miR-372 (position 575-581 of p40 3' UTR) miR-182 (position 1276-1283 of p40 3' UTR) miR-183 (position 52-58 of p40 3' UTR) miR-223 (position 774-781 of p40 3' UTR)



Increased miR-106b in mesenchymal-like cells silences BRMS1L.

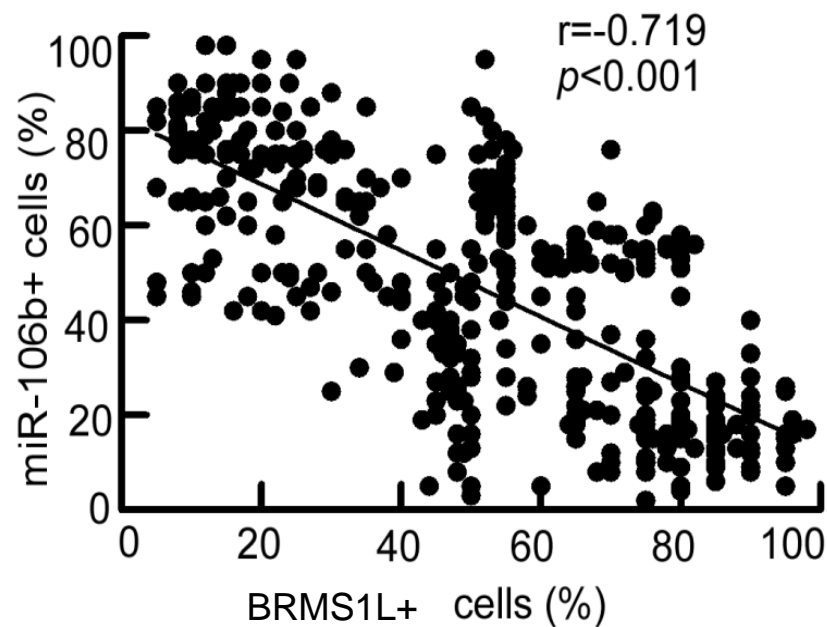
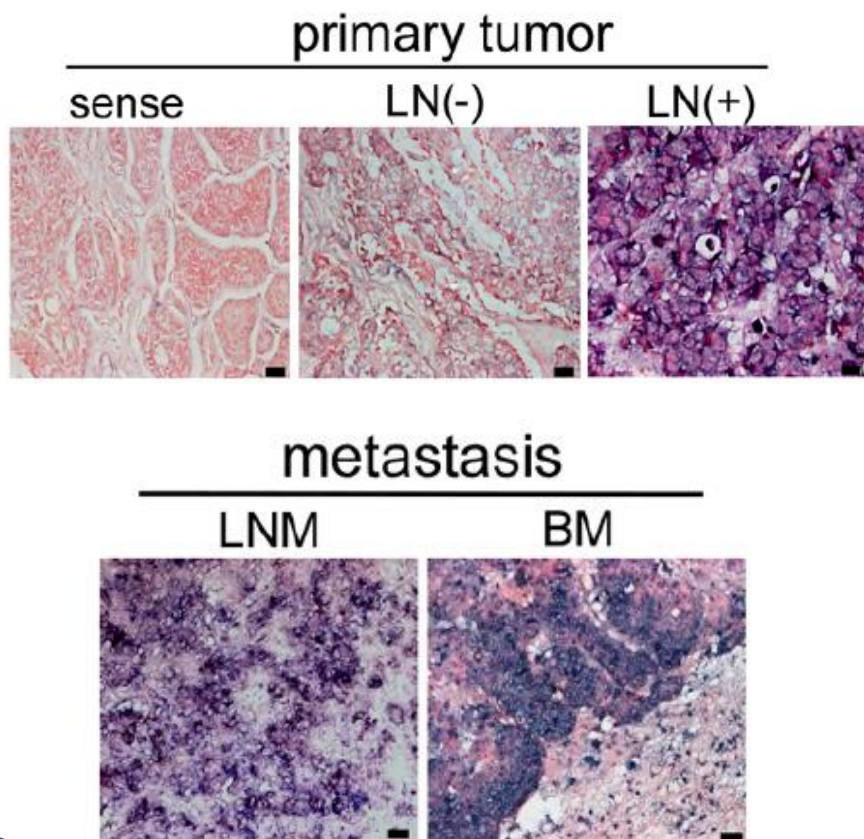


miR-106b suppresses Wnt pathway and EMT by targeting BRMS1L.



miR-106b expression is inversely correlated with BRMS1L.

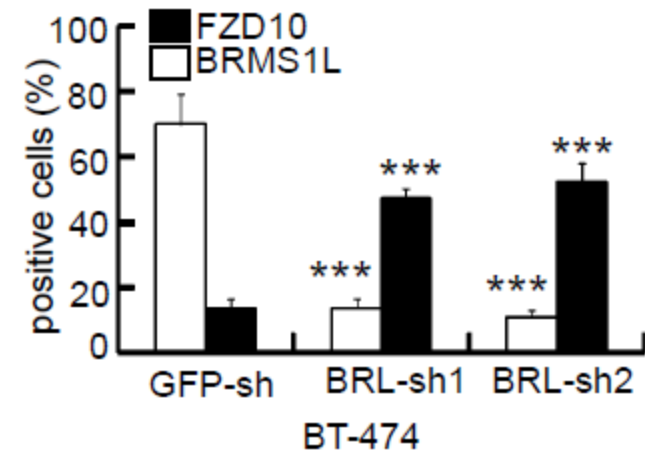
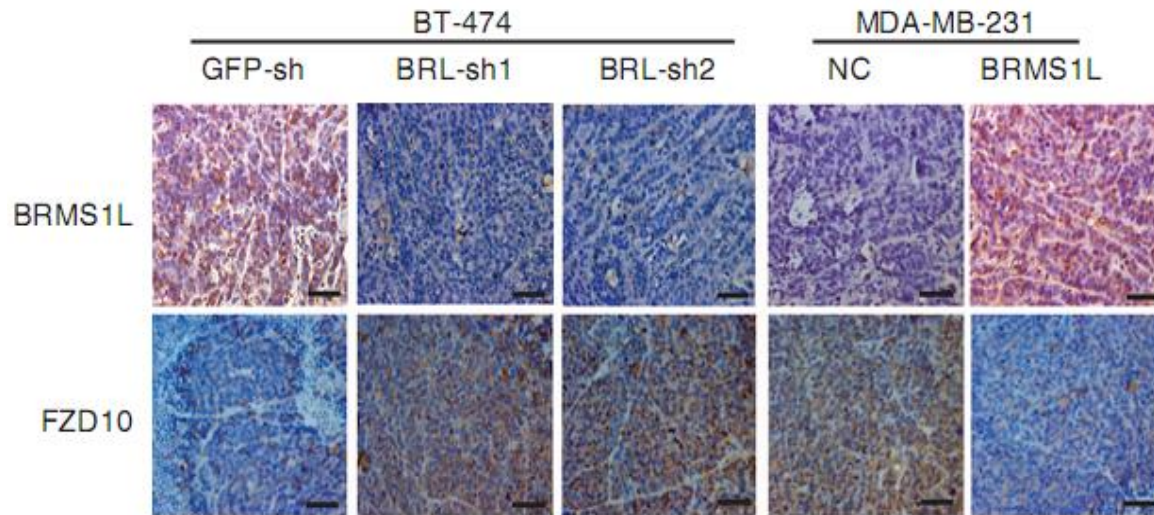
ISH:106b





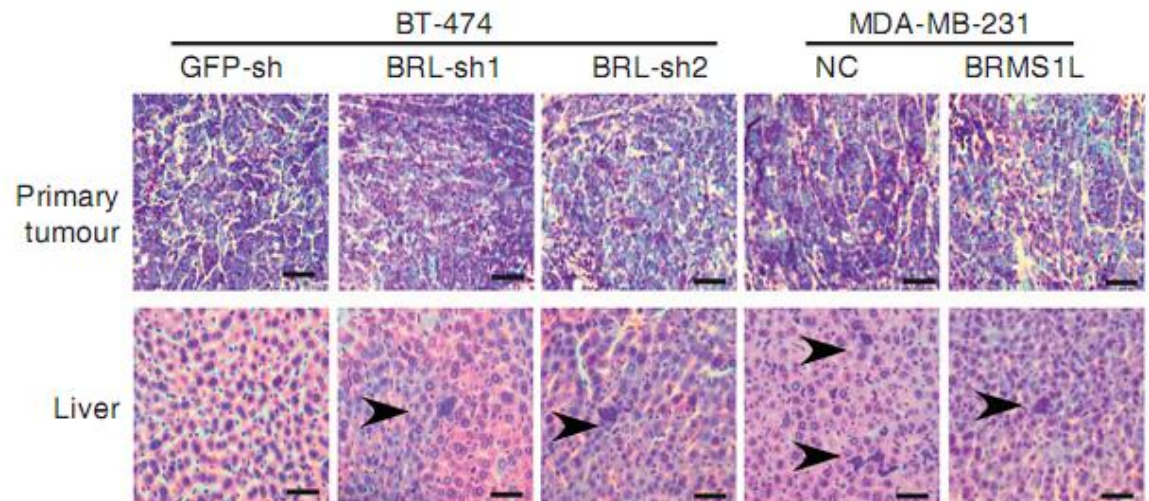
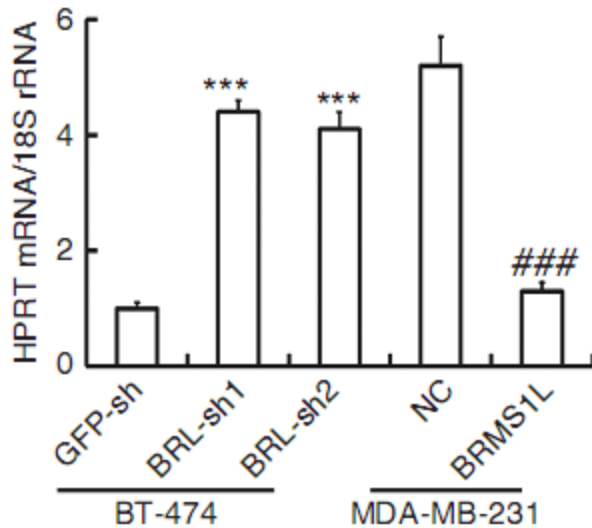
miR-106b activates Wnt/ β -catenin signaling and promotes EMT by silencing BRMS1L in breast cancer.

Expression of BRMS1L and FZD10 in xenografts

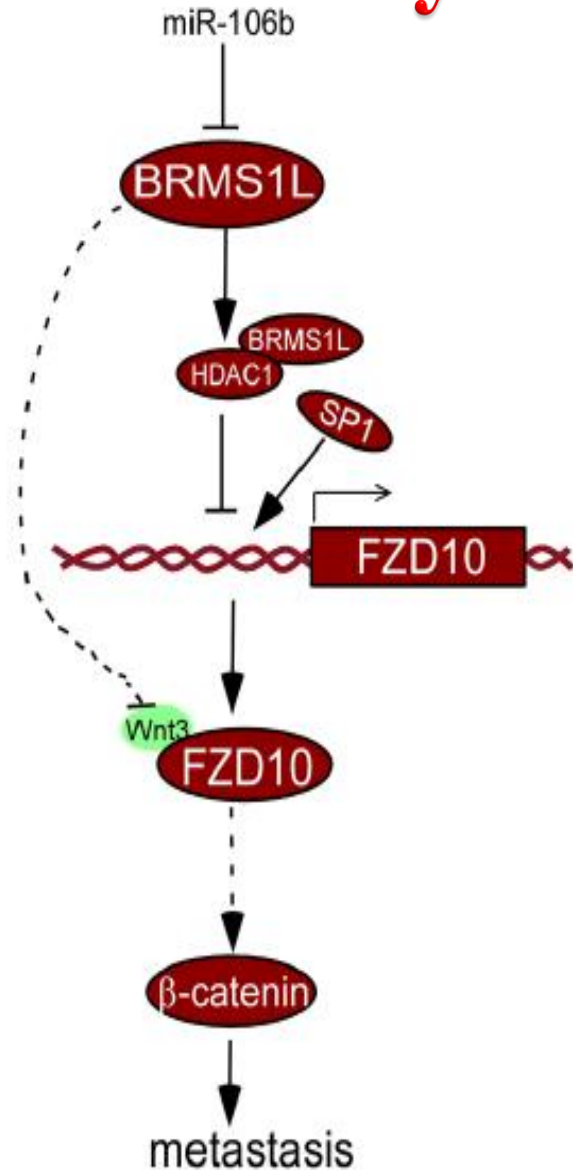


BRMS1L significantly inhibits liver metastasis

BT-474 (5×10^6)			MDA-MB-231 (2×10^6)		
Groups	Tumors	Liver metastasis	Groups	Tumors	Liver metastasis
GFP-sh	7/8	1/8	NC-vec	8/8	6/8
BRL-sh1	6/8	4/8	BRL	7/8	2/8
BRL-sh2	7/8	5/8			



Summary



Significance

Our findings highlight the contribution of BRMS1L in epigenetic silencing of oncogenes and its effect in tumor suppression.

Acknowledgements



973 Projects from Ministry of Science and Technology of China

Natural Science Foundation of China

Erwei Song

Shaohua Qu

Xiao-Bin Iv

Bodu Liu



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