Protein acylation and tumor progression

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School of Basic Medical Sciences
and International Cancer Institute

September 24, 2021

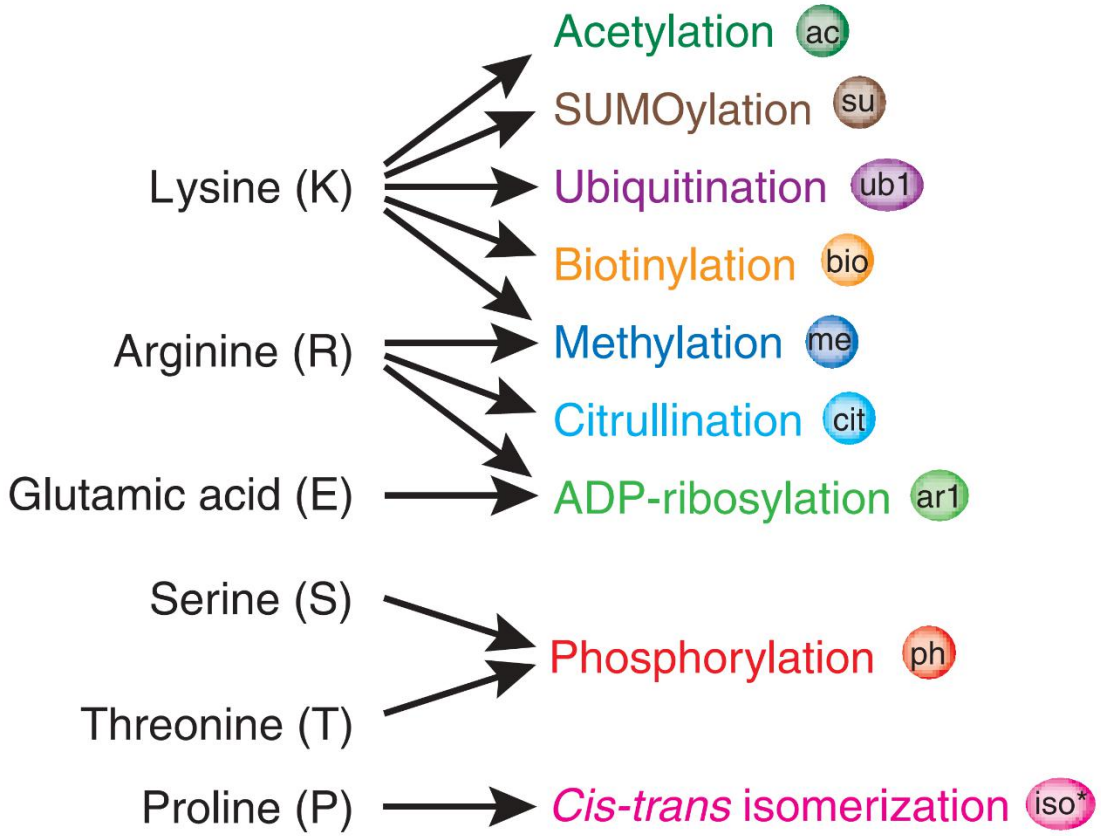
Modifications of Biomolecules

- DNA： <10
- RNA： >100
- Proteins： >500

Total modifications in human: $>10^{17}$

New chemical bonds formation

Commonly seen PTMS



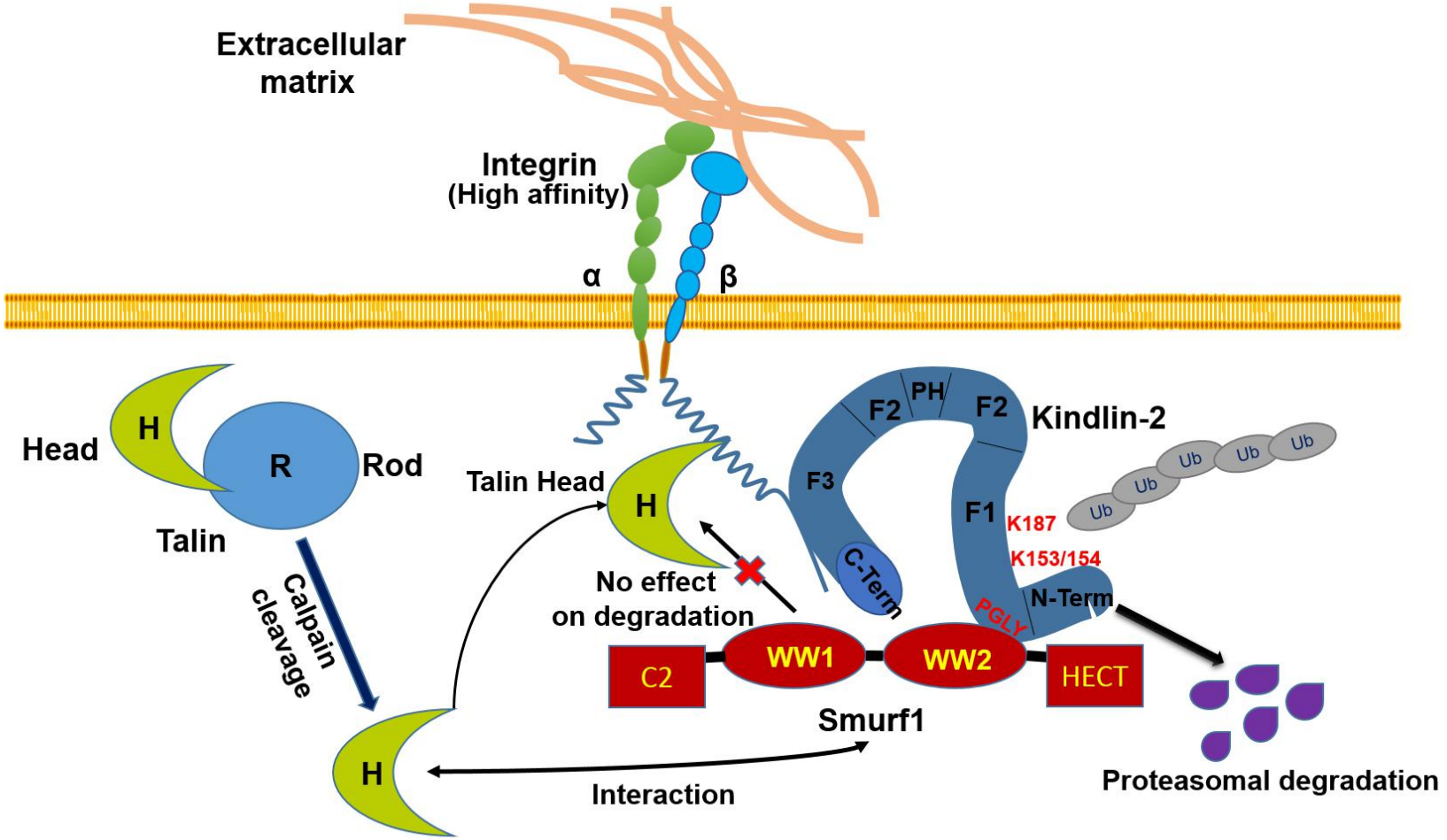
Nat Struct Mol Biol. 2007，14:1017-24

Part 1

Protein PTMs change their structure, biological functions and roles in the disease develoment

Smurf1 inhibits integrin activation by controlling Kindlin-2 ubiquitination and degradation

Xiaofan Wei,[1]* Xiang Wang,[1]* Jun Zhan,[1] Yuhan Chen,[3] Weigang Fang,[2] Lingqiang Zhang,[3] and Hongquan Zhang[1]

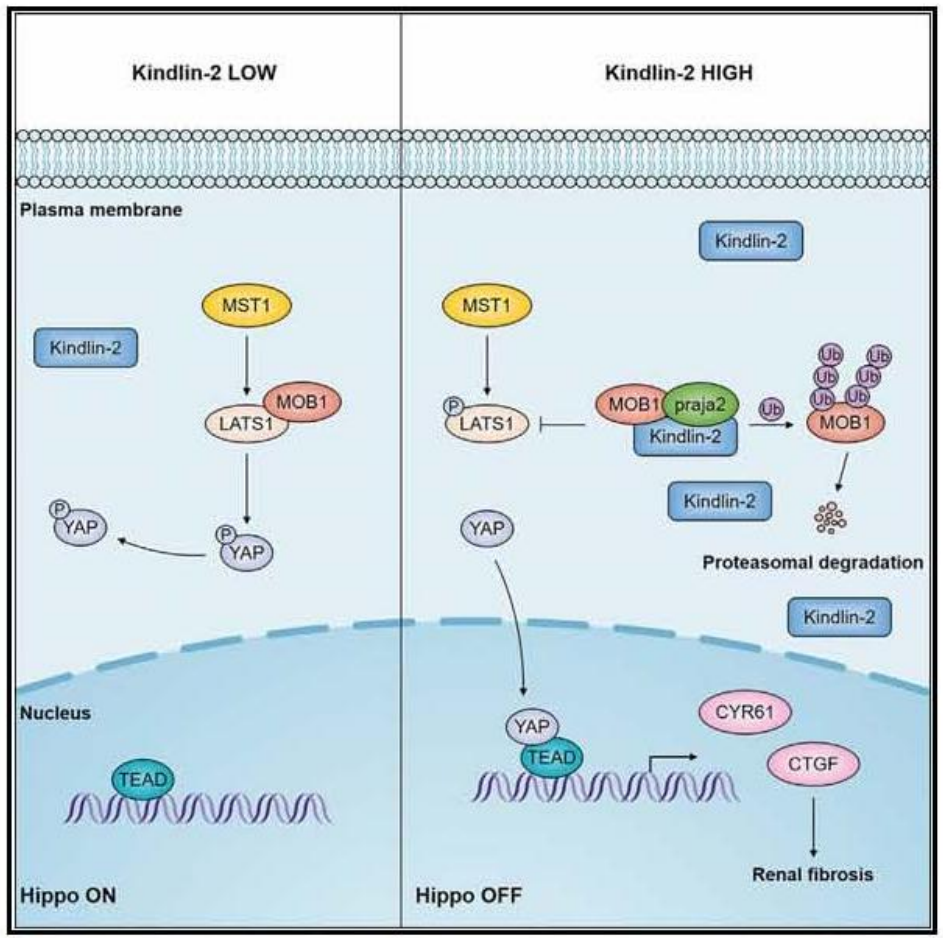


Journal of Cell Biology, 2017

Cell Reports

Kindlin-2 Inhibits the Hippo Signaling Pathway by Promoting Degradation of MOB1

Graphical Abstract



Authors

Jiagui Song, Tianzhuo Wang, Xiaochun Chi, ..., Yunling Wang, Jun Zhan, Hongquan Zhang

Correspondence

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In Brief

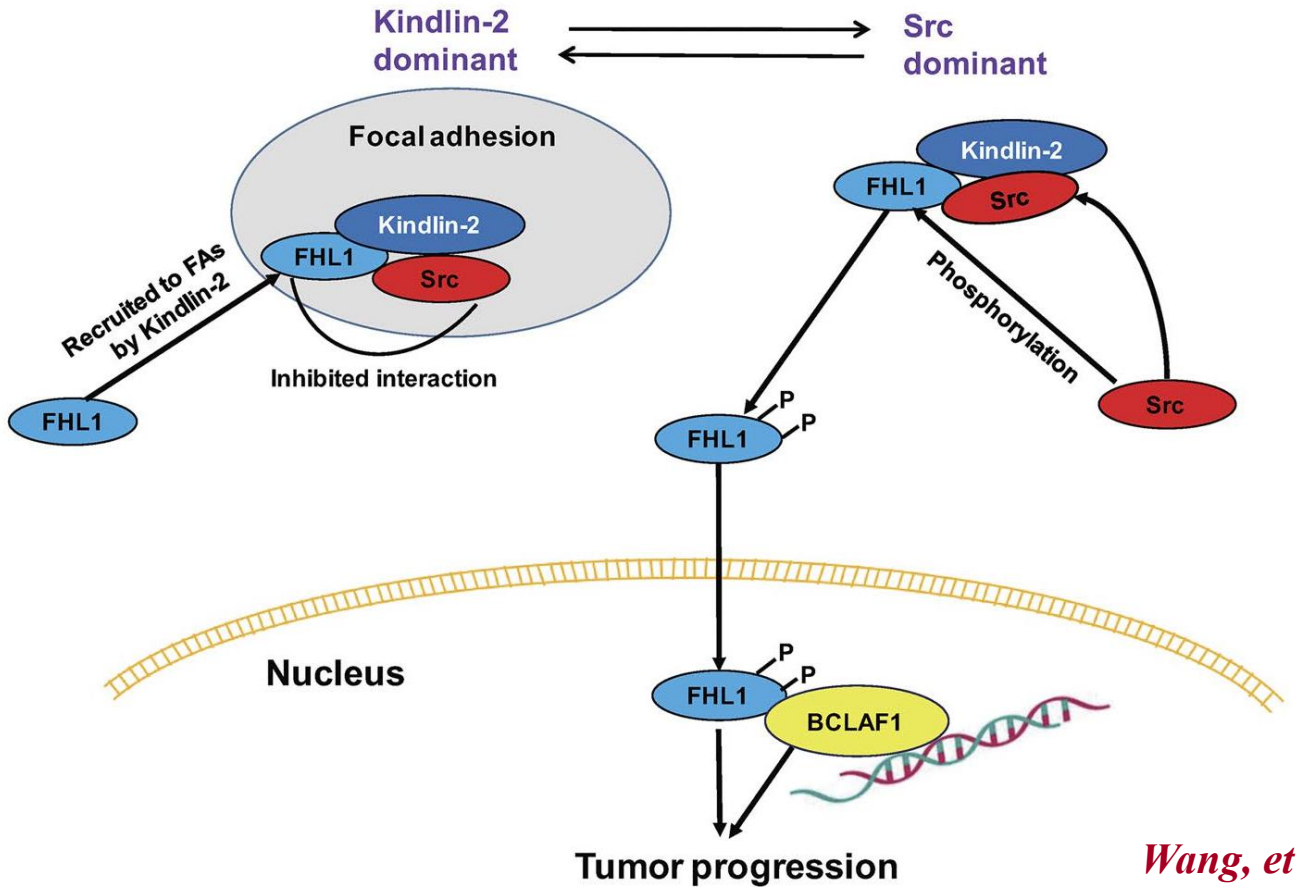
Song et al. demonstrate that Kindlin-2 inhibits Hippo pathway by enhancing the interaction between MOB1 and E3 ligase praja2 and promoting MOB1 degradation. Kindlin-2 depletion activates the Hippo pathway and alleviates renal fibrosis in UUO mouse model. A specific long-lasting siRNA against Kindlin-2 is of therapeutic value for renal fibrosis.

Song, et al. Cell Reports, 2019.

JCB Published Online: 6 February, 2018 | Supp Info: http://doi.org/10.1083/jcb.201708064

Src-mediated phosphorylation converts FHL1 from tumor suppressor to tumor promoter

Xiang Wang,[1]* Xiaofan Wei,[1]* Yang Yuan,[1] Qingrui Sun,[1] Jun Zhan,[1] Jing Zhang,[1] Yan Tang,[1] Feng Li,[1] Lihua Ding,[2] Qinong Ye,[2] and Hongquan Zhang[1]



Wang, et al. Journal of Cell Biology, 2018.

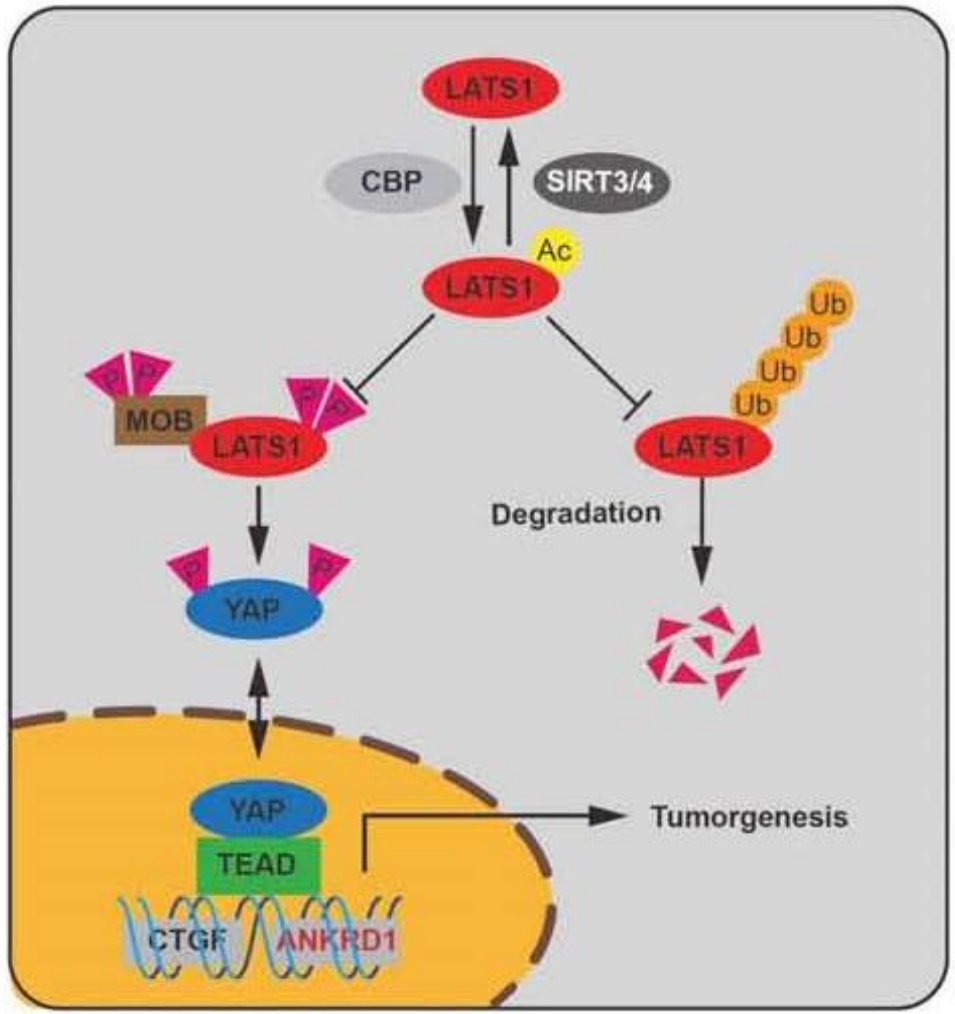
SCIENCE CHINA
Life Sciences

•RESEARCH PAPER•

https://doi.org/10.1007/s11427-020-1914-3

LATS1 K751 acetylation blocks activation of Hippo signalling and switches LATS1 from a tumor suppressor to an oncoprotein

Siyuan Yang[1], Weizhi Xu[1], Cheng Liu[1], Jiaqi Jin[1], Xueying Li[1], Yuhan Jiang[1], Lei Zhang[1], Xianbin Meng[2], Jun Zhan[1] & Hongquan Zhang[1*]



Yang, et al. Sci.Chin.Lif.Sci. 2021.

Part 2

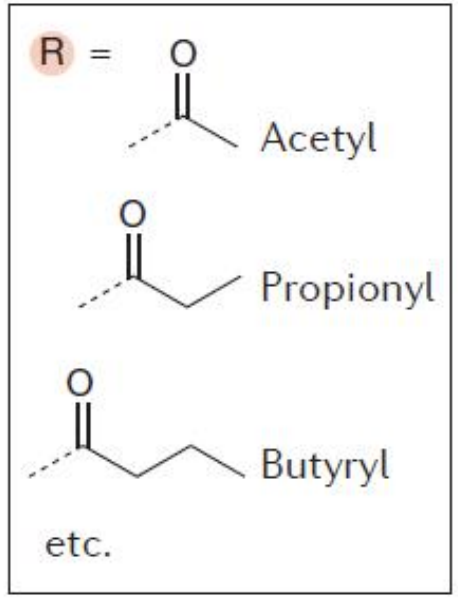
Precise prognosis for cancer patients based on protein acetylation

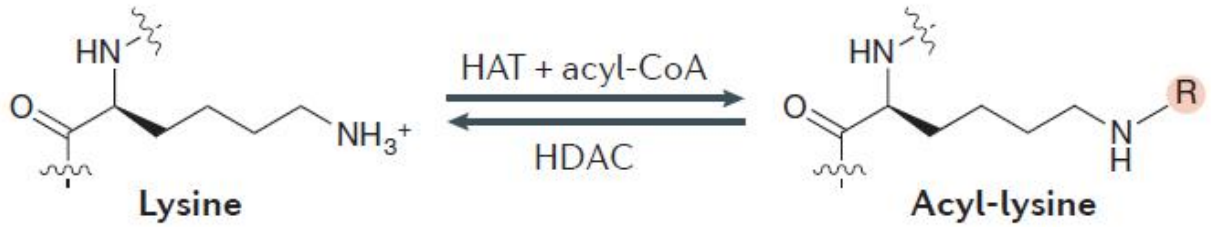
Acetylation of transcription factor HOXB9 inhibits lung adenocarcinoma progression

Dr. Junhu Wan

Acylation 酰基化修饰

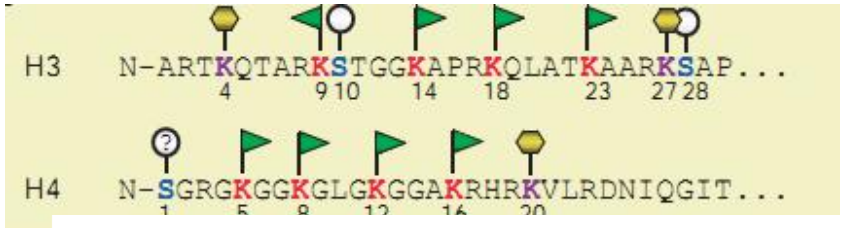
- Acetylation: 乙酰化
- Propionylation: 丙酰化
- Butyrylation: 丁酰化
- Crotonylation: 巴豆酰化
- 2-Hydroxyisobutyrylation: 2-羟基异丁酰化
- β-Hydroxybutyrylation: β-羟基丁酰化
- Malonylation: 丙二酰化
- Succinylation: 琥珀酰化
- Glutarylation: 戊二酰化

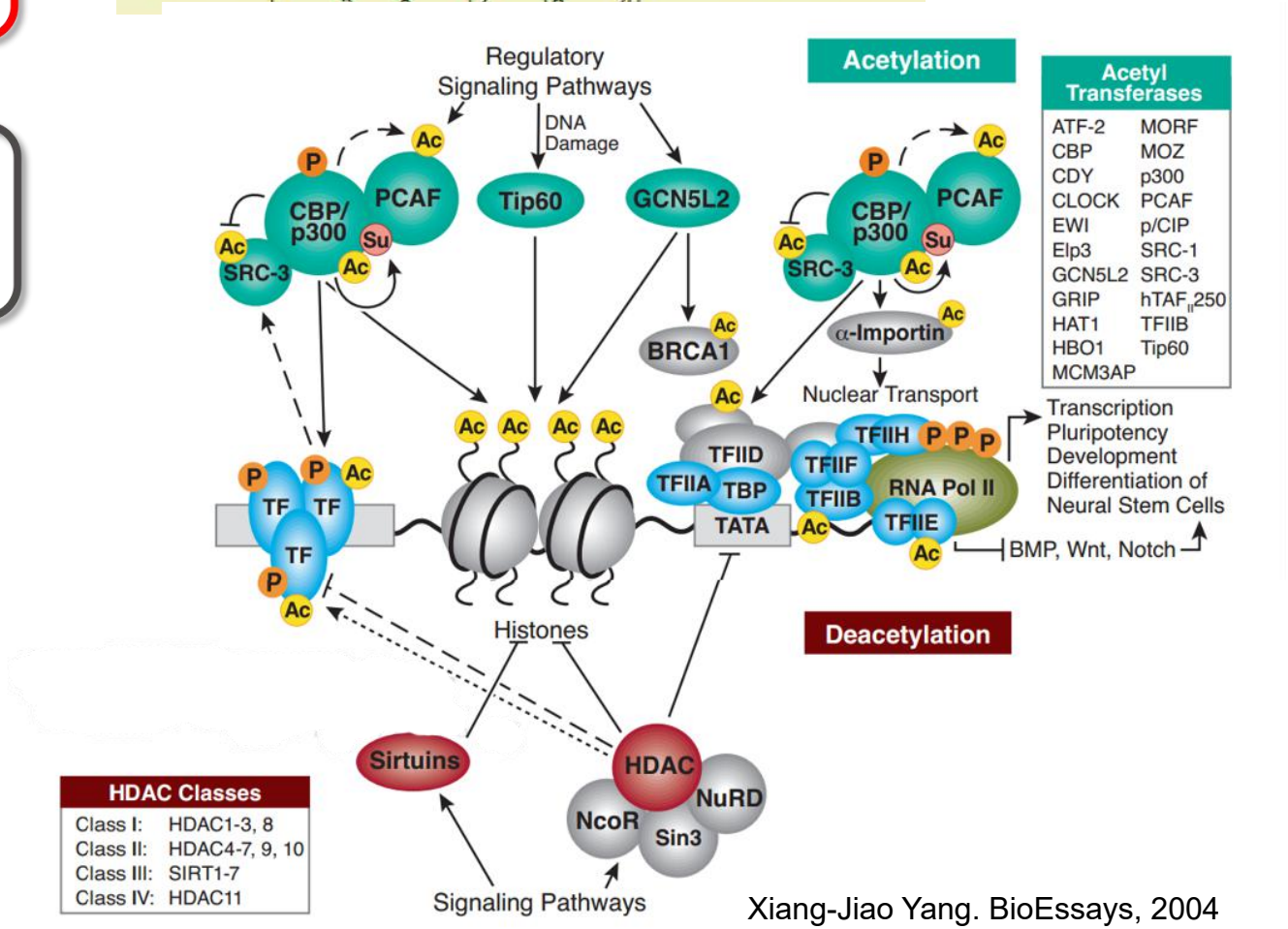




Acetylation

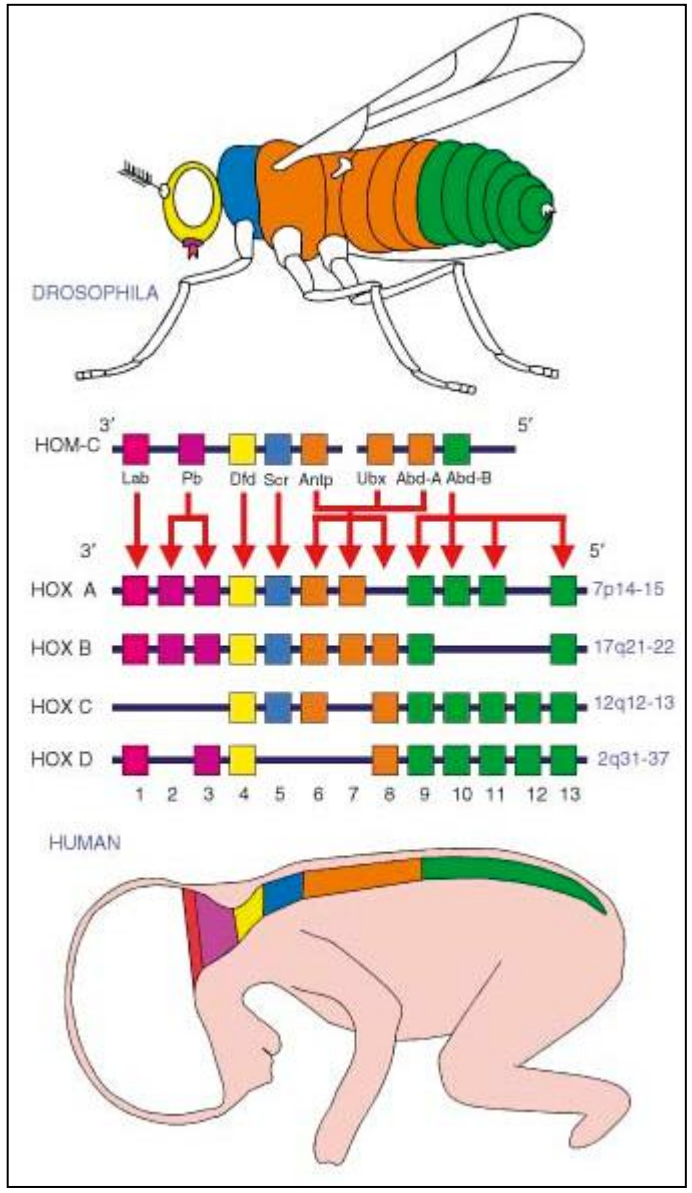
- Histone
- Non-Histone





Xiang-Jiao Yang. BioEssays, 2004

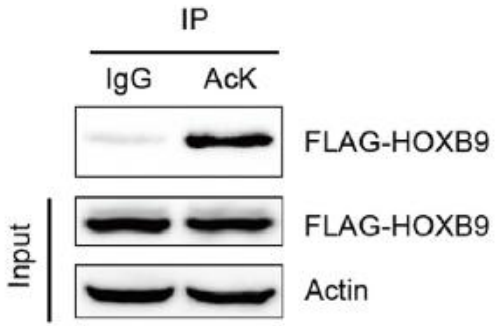
HOX gene family

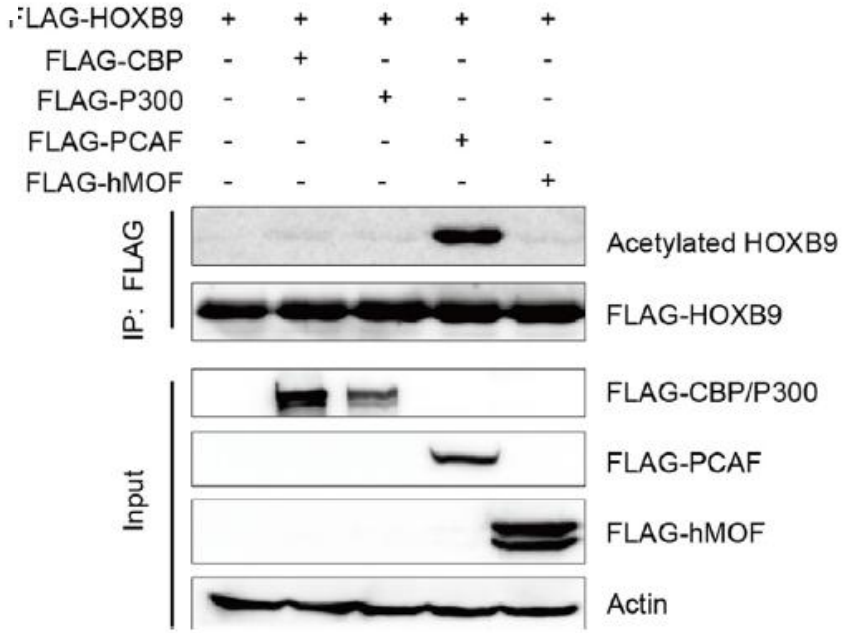


- In human, 39 HOX genes are found in four clusters assigned to 13 paralog groups in each cluster
- HOX genes are expressed in temporal and spatial collinearity
- HOX genes have crucial roles in development,regulating apoptosis,receptor signaling, differentiation,motility and angiogenesis

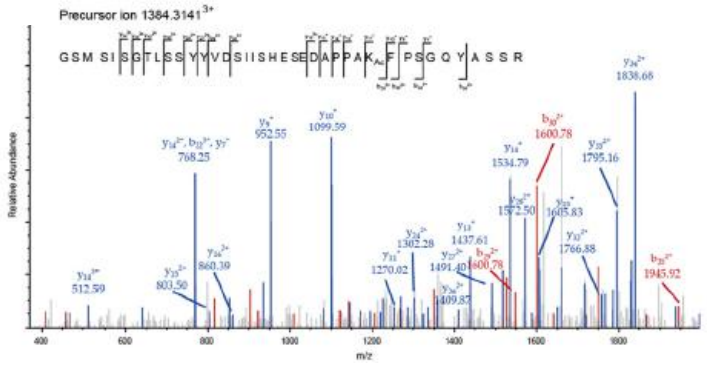
DG Grier et al. The pathophysiology of HOX genes and their rolein cancer. J Pathol

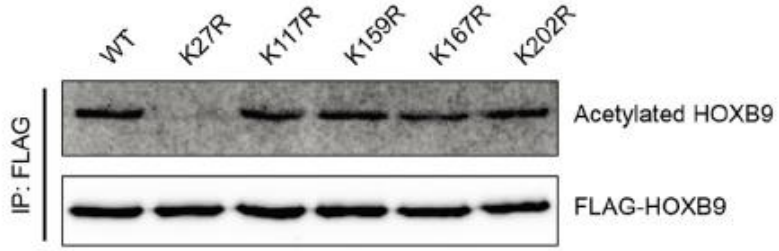
HOXB9 interacts with and is acetylated by acetyltransferase PCAF





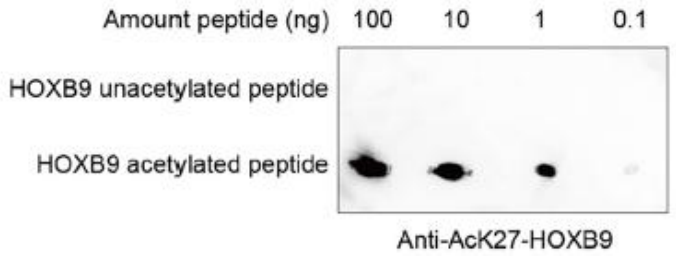
HOXB9 is acetylated at residue K27 by PCAF

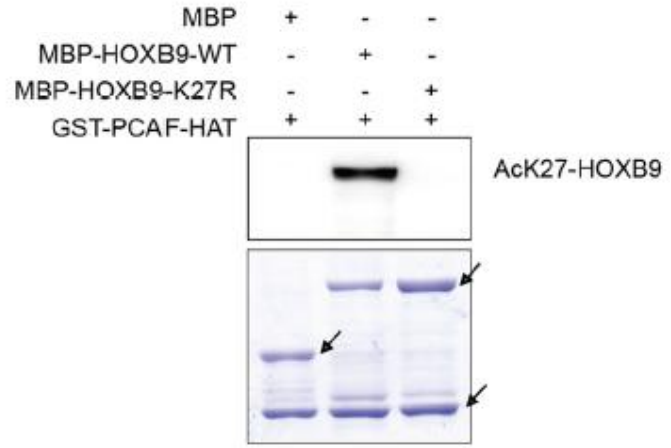


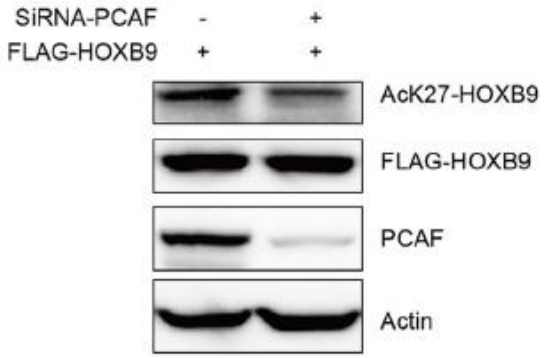


Homo sapiens (Human)	SEDAPPAKFPS	30
Ailuropoda melanoleuca (Giant panda)	SEDAPPAKFPS	30
Bos taurus (Bovine)	SEDAPPAKFPS	30
Canis familiaris (Dog)	SEDAPPAKFPS	30
Mus musculus (Mouse)	SEDAPPAKFPS	30
Rattus norvegicus (Rat)	SEDAPPAKFPS	30
Sus scrofa (Pig)	SEDAPPAKFPS	30
Xenopus laevis (African clawed frog)	TDETPAAKFSA	30

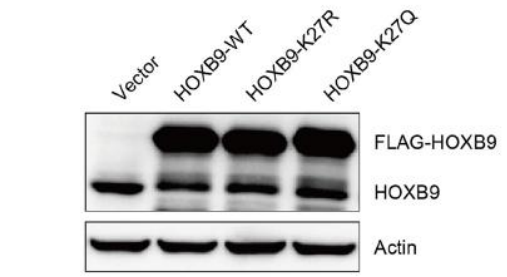
HOXB9 is acetylated at residue K27 by PCAF

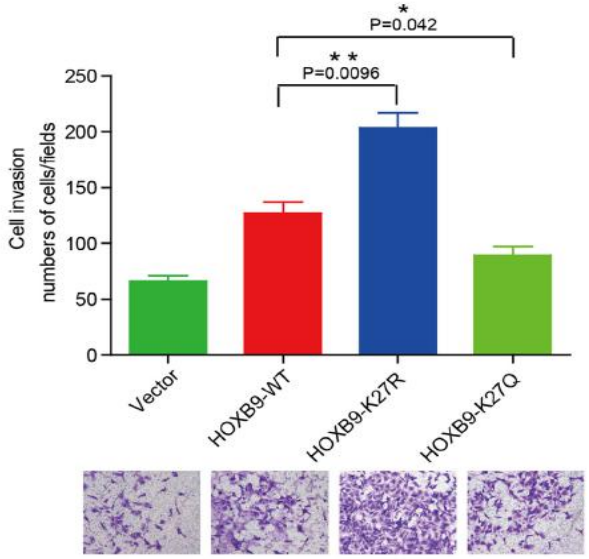


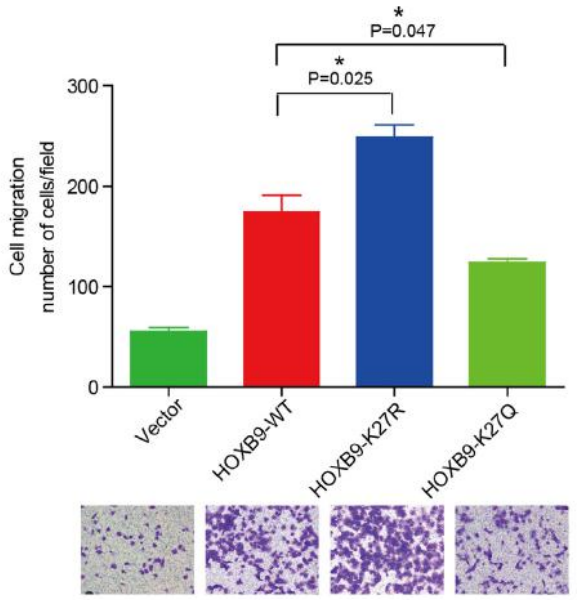




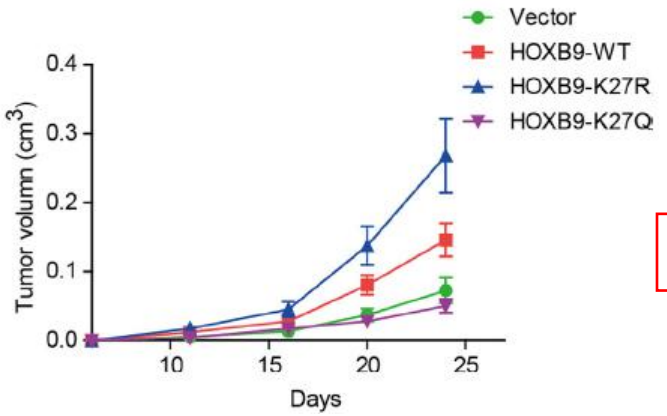
Acetylation of HOXB9 suppresses lung cancer cell migration and invasion

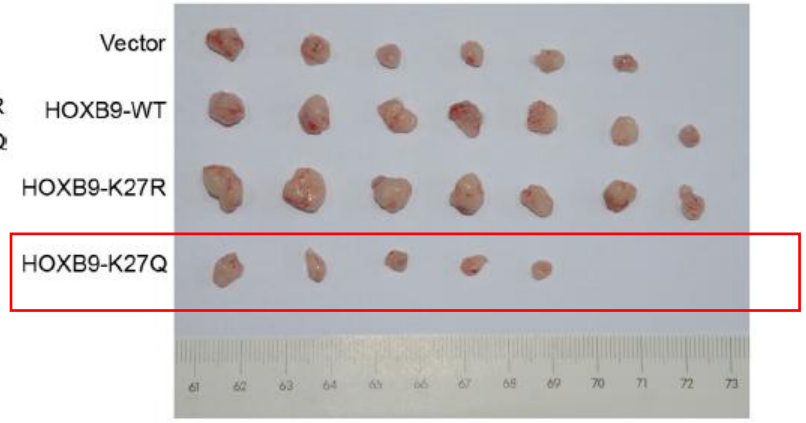


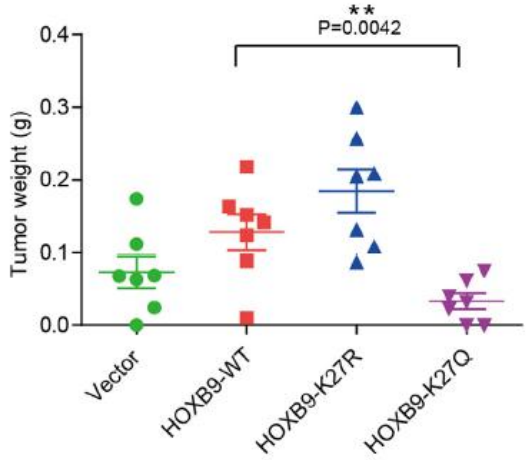




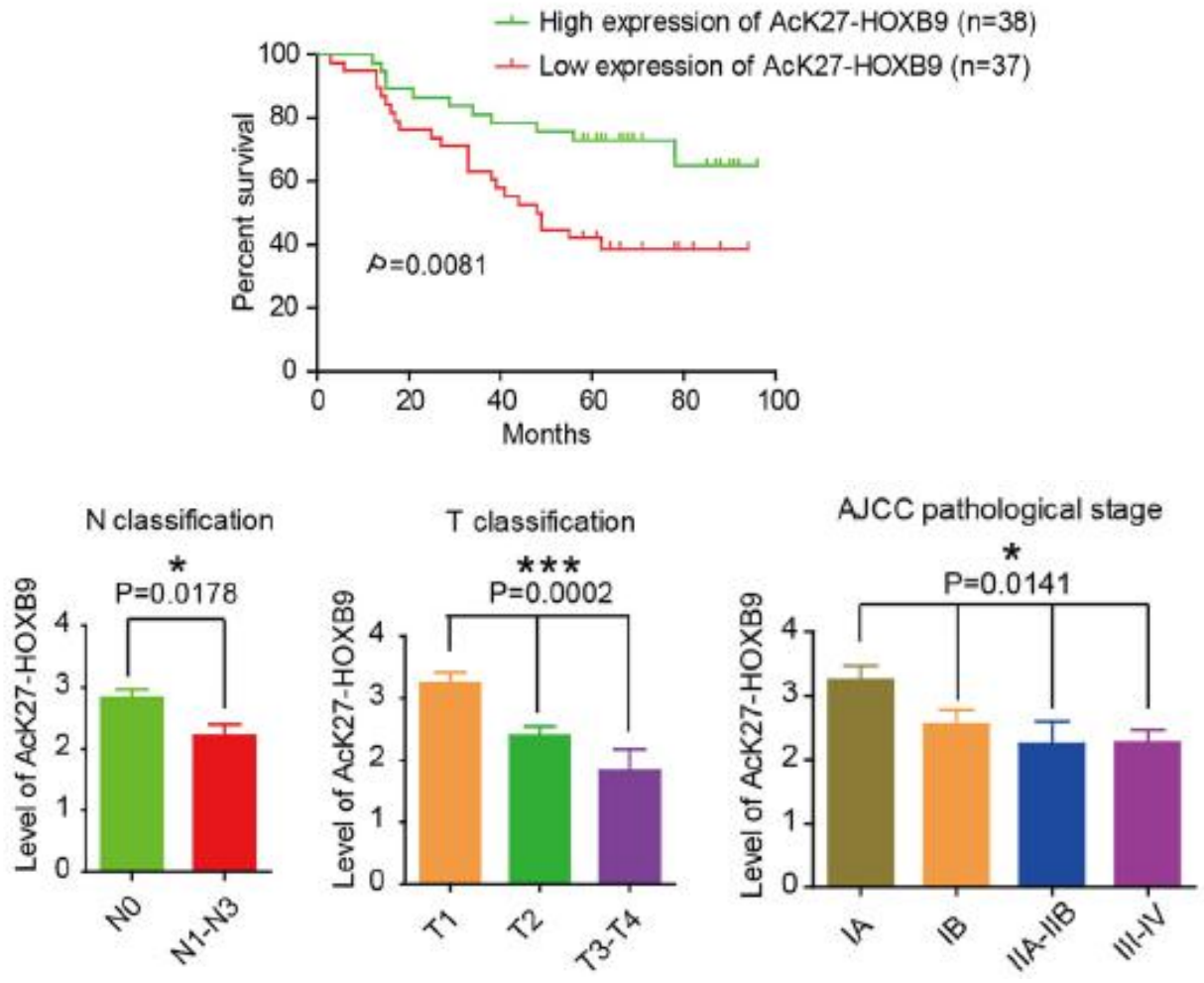
Acetylation of HOXB9 suppresses lung cancer xenografted tumor growth



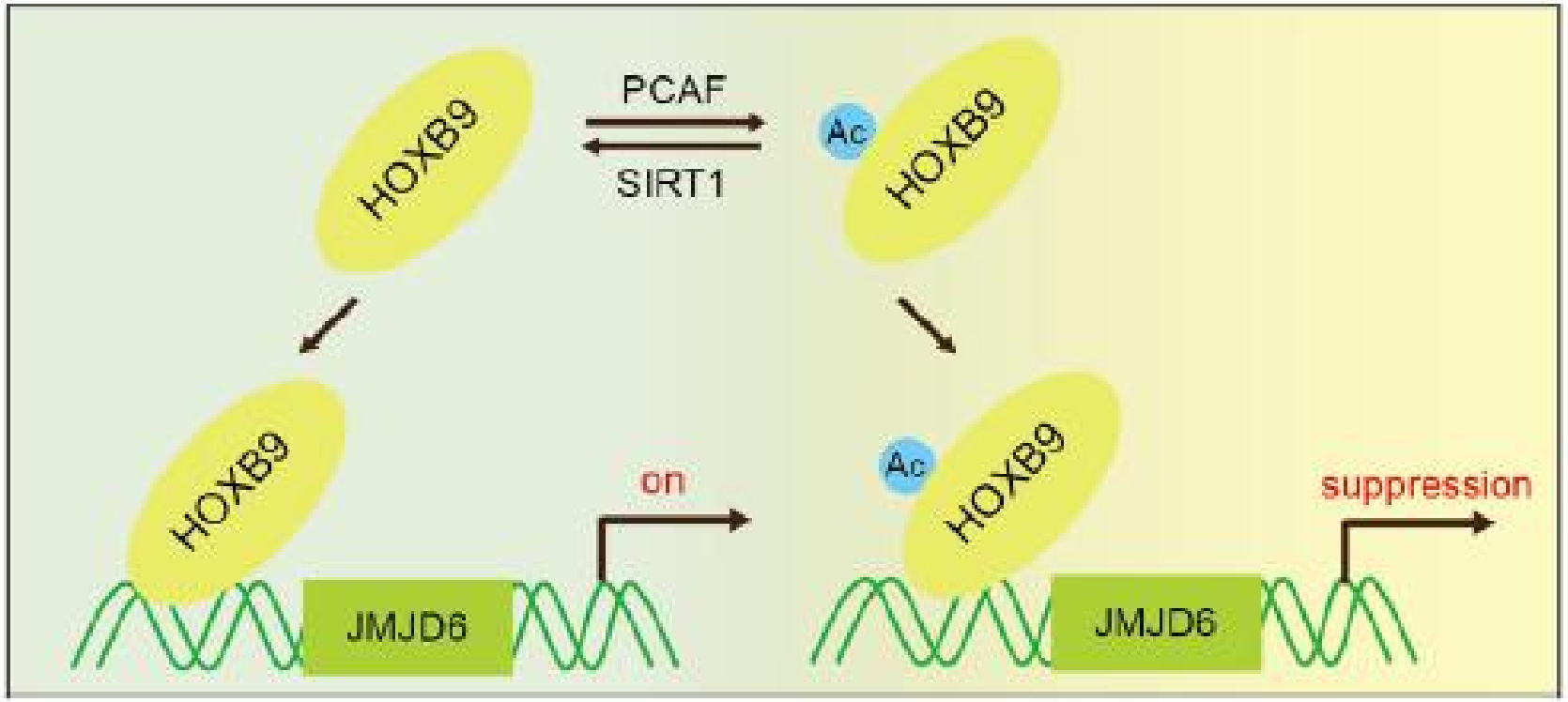




Elevated K27 acetylation of HOXB9 predicts a favorable survival in lung cancer patients



Acetylation of HOXB9 inhibits tumor progression via suppression of JMJD6

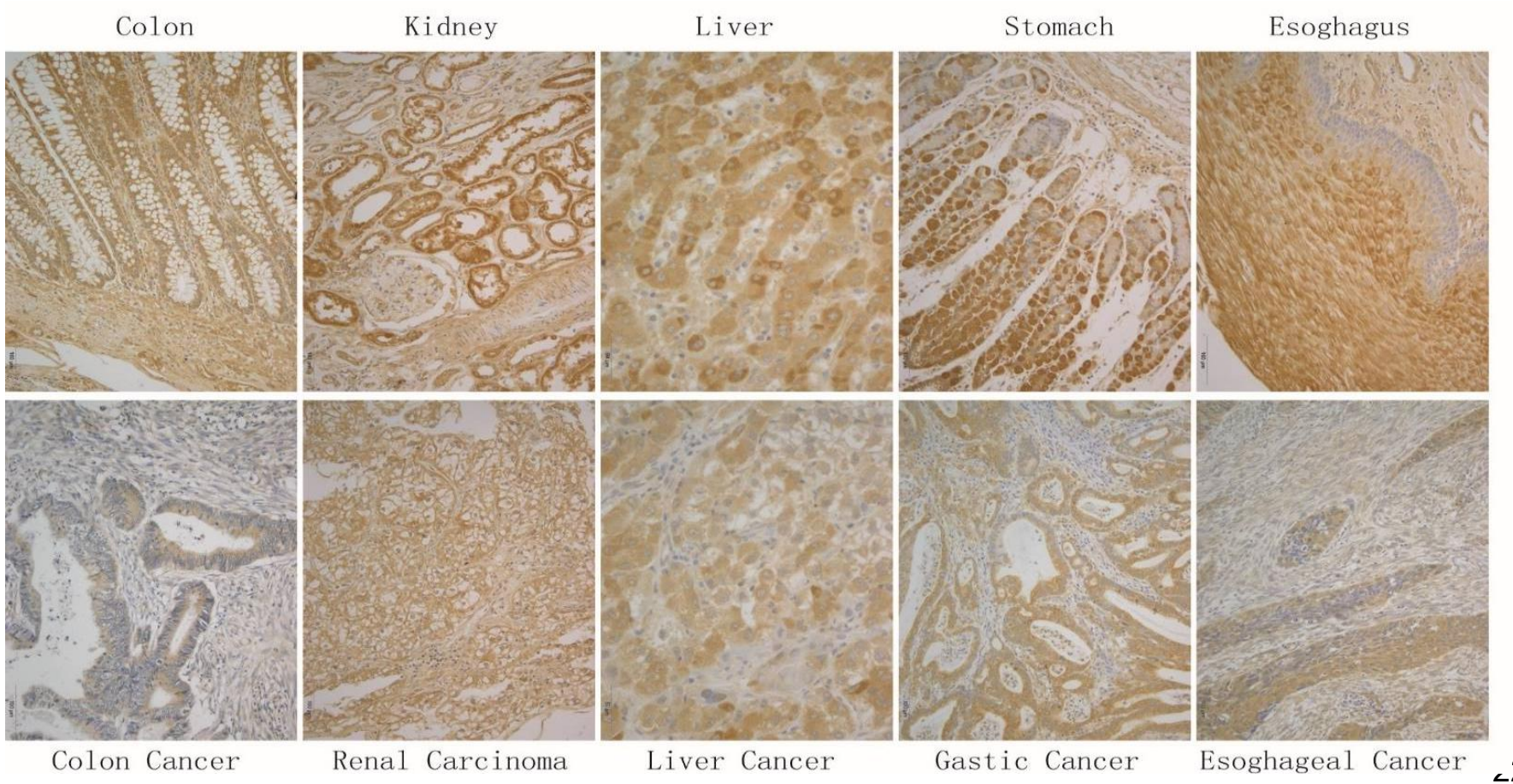


Wan，et al. Nucleic Acids Research 43: 3591–3604, 2016.

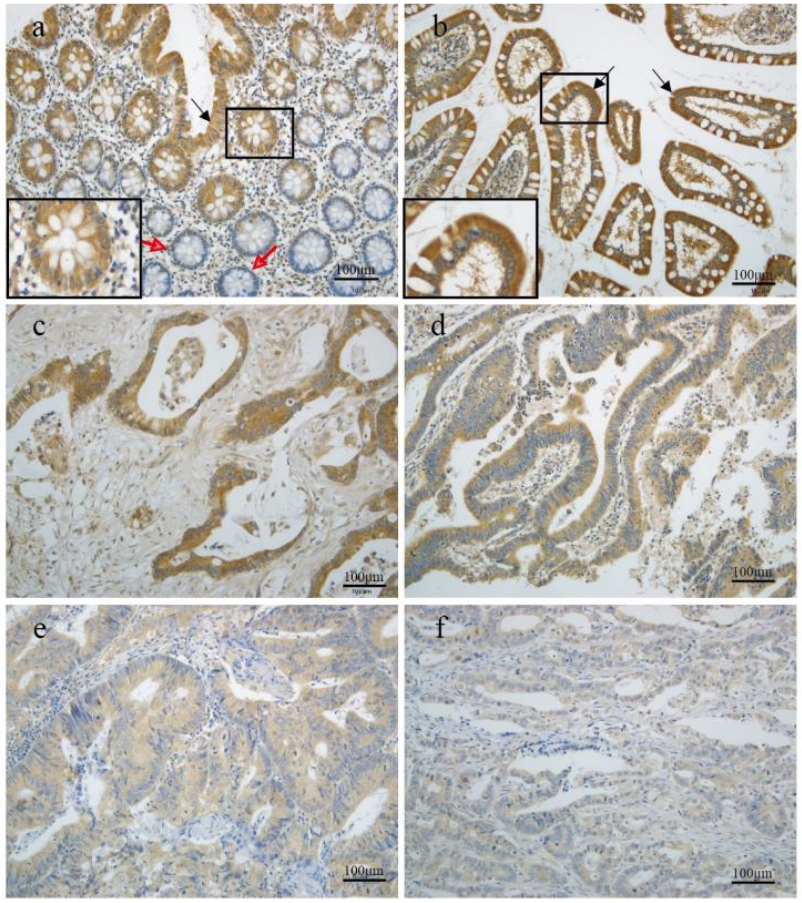
Acetylation of HOXb9 at K27 inhibits CRC progression

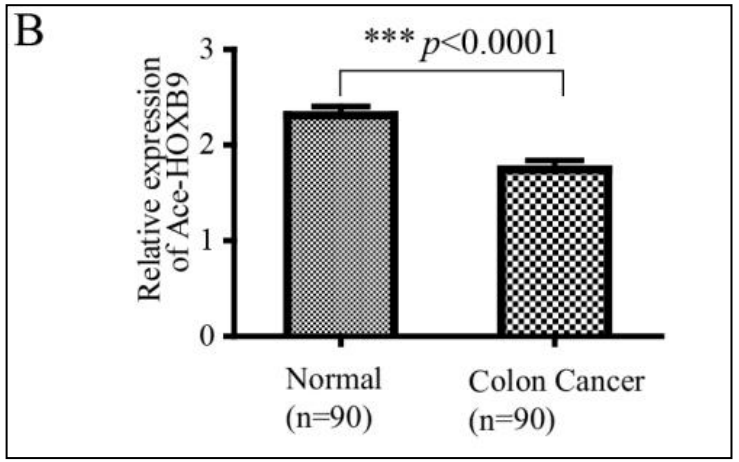
Dr. Jun Zhan

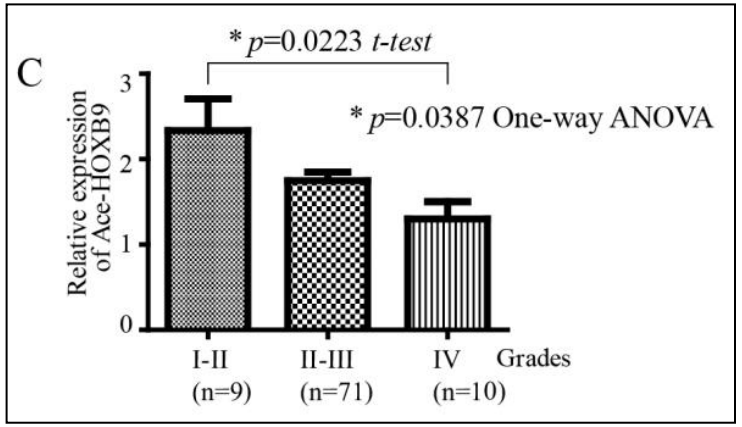
AcK27-HOXB9 was downregulated in multiple cancers



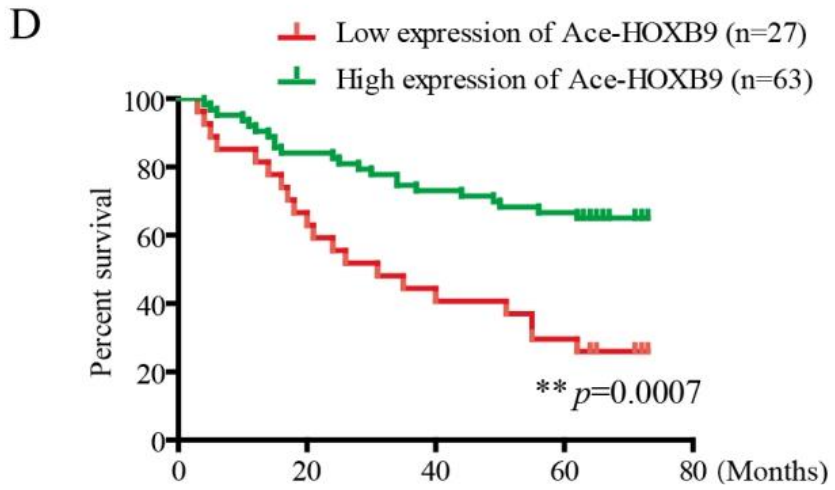
AcK27-HOXB9 predicts a favourable outcome in colon cancer patients

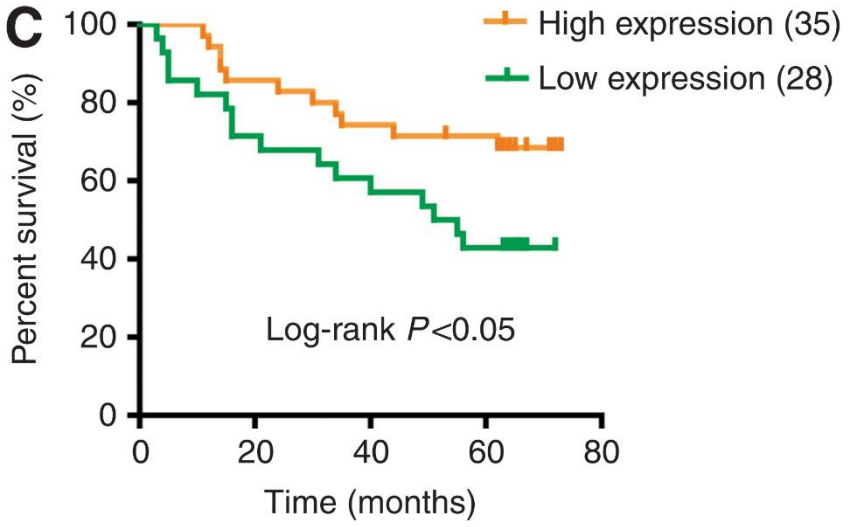




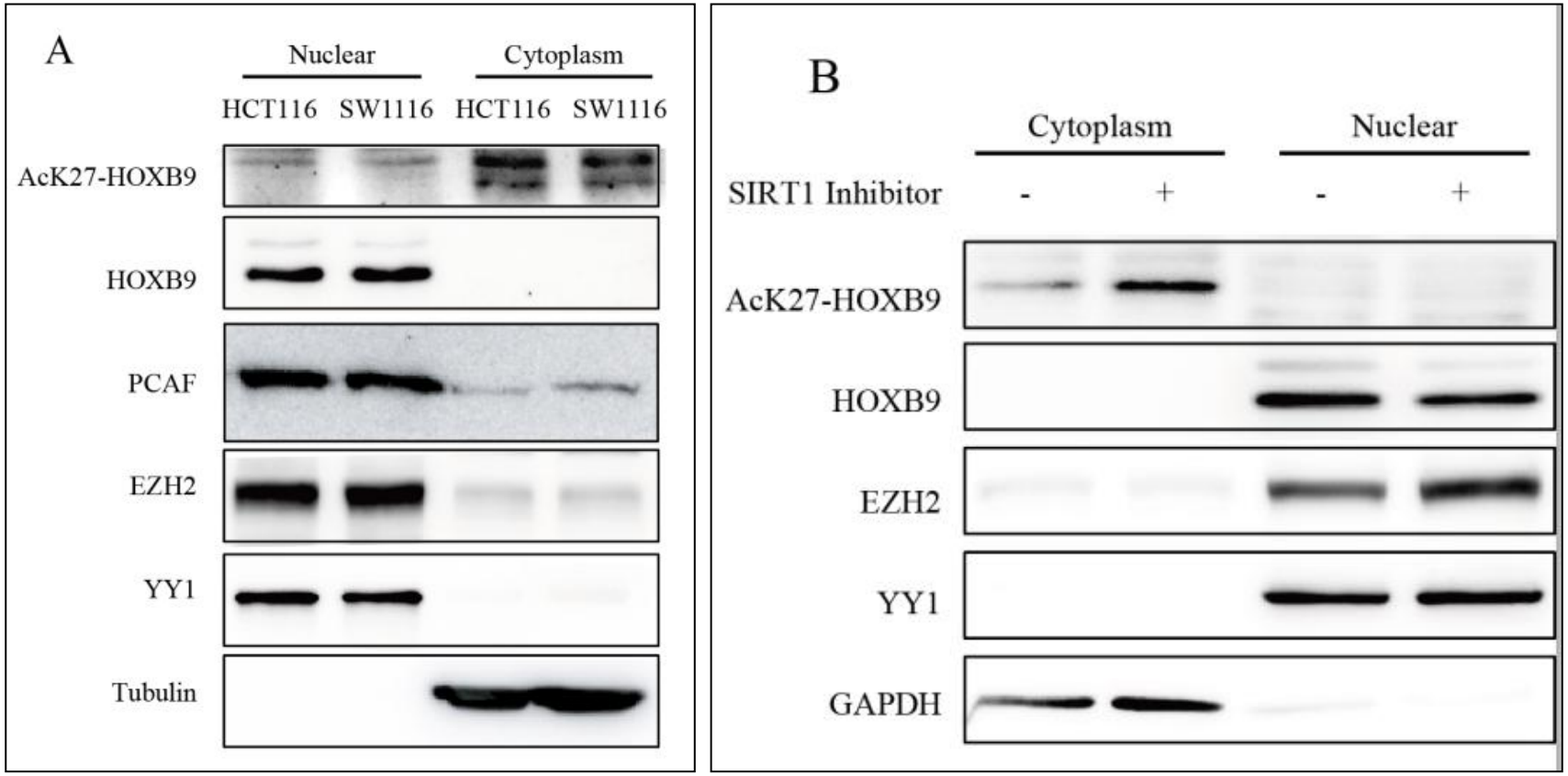


AcK27-HOXB9 predicts a favourable outcome in colon cancer patients

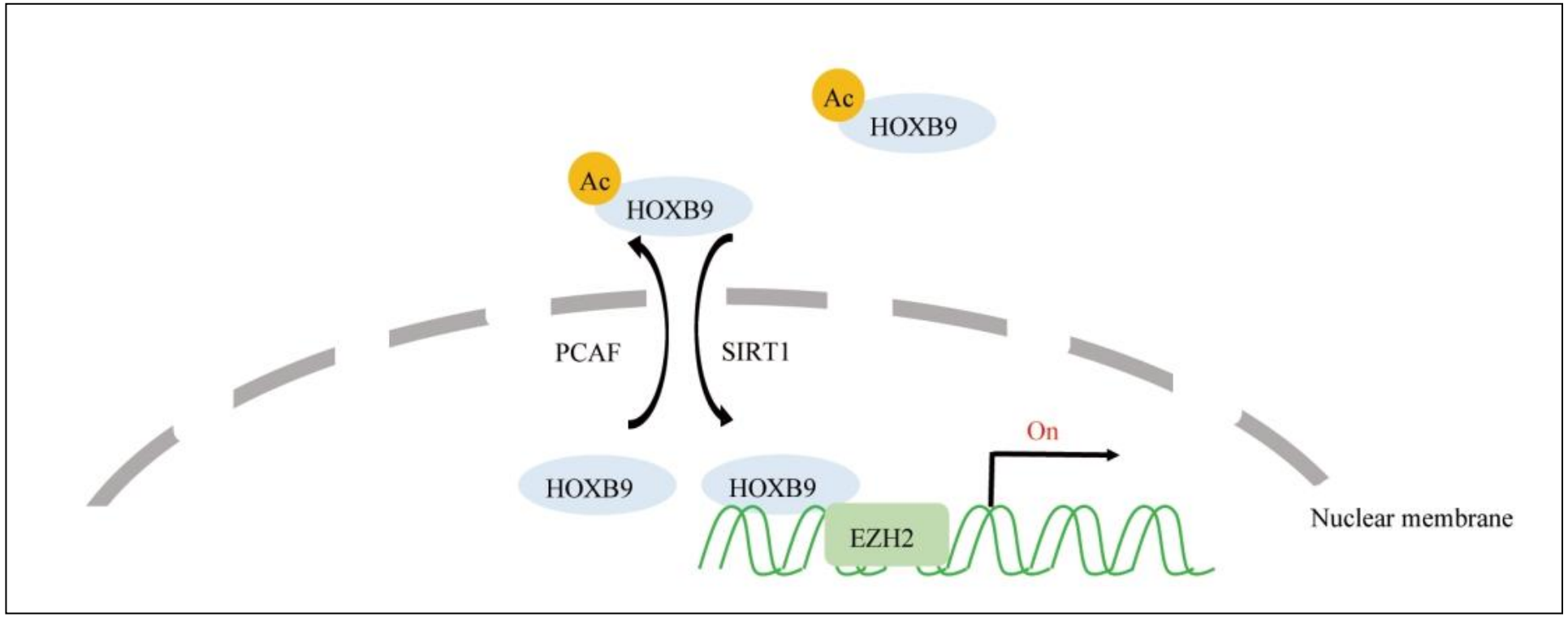




Acetylated HOXB9 translocates from nucleus to cytoplasm



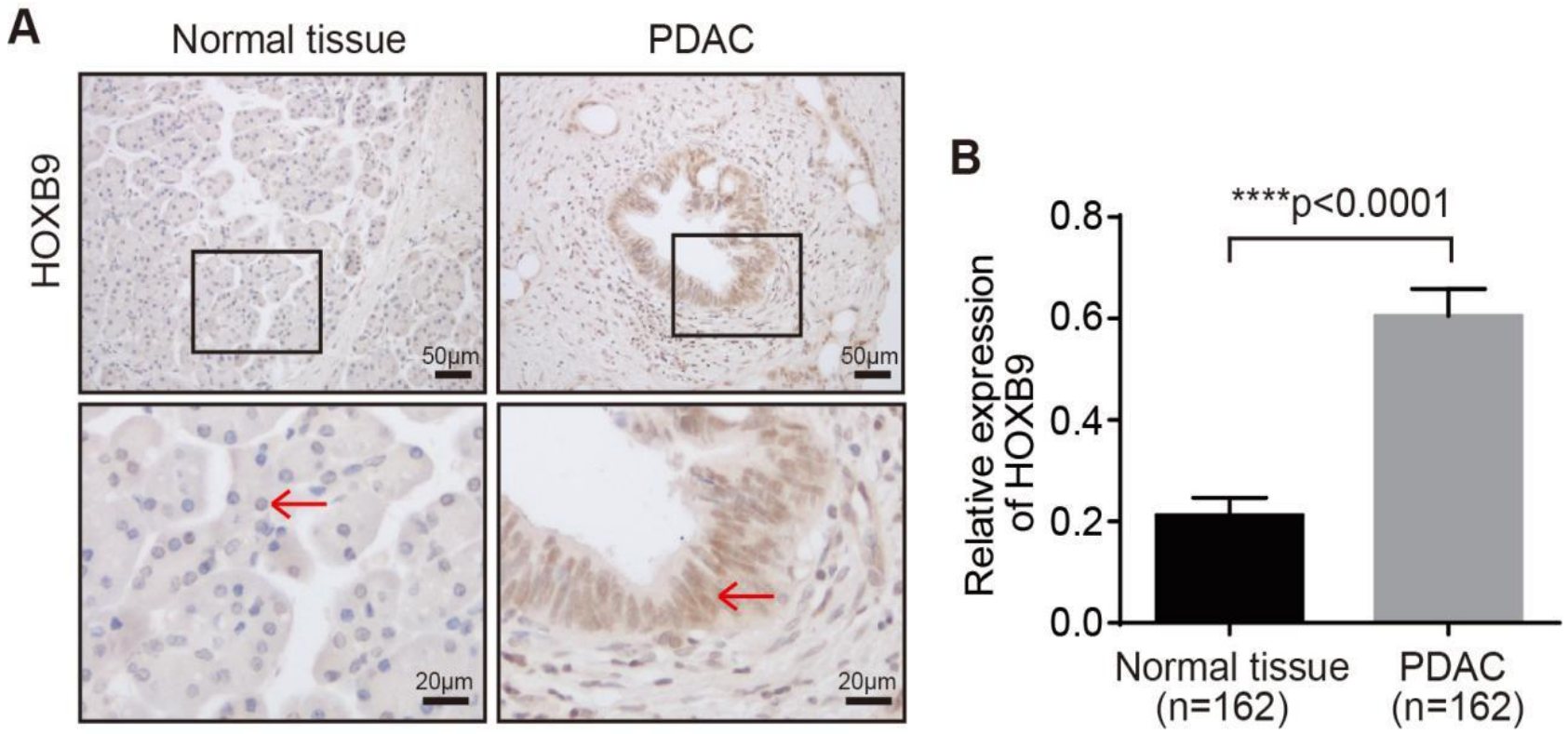
Acetylated HOXB9 translocates to cytoplasm and inhibits tumor growth



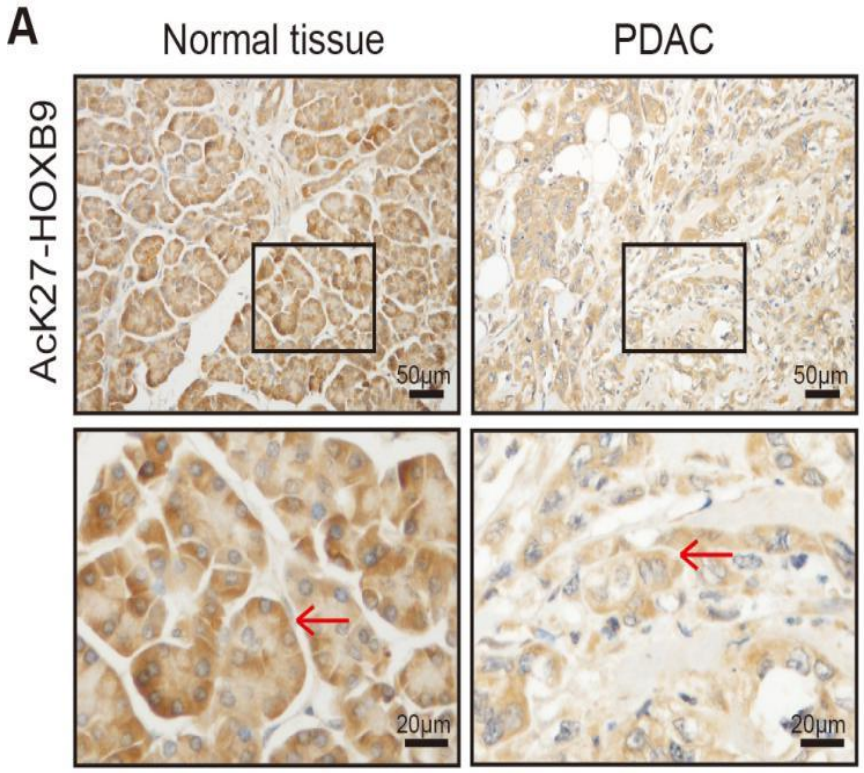
Acetylation of HOXB9 at K27 predicts well prognosis in PDAC patients

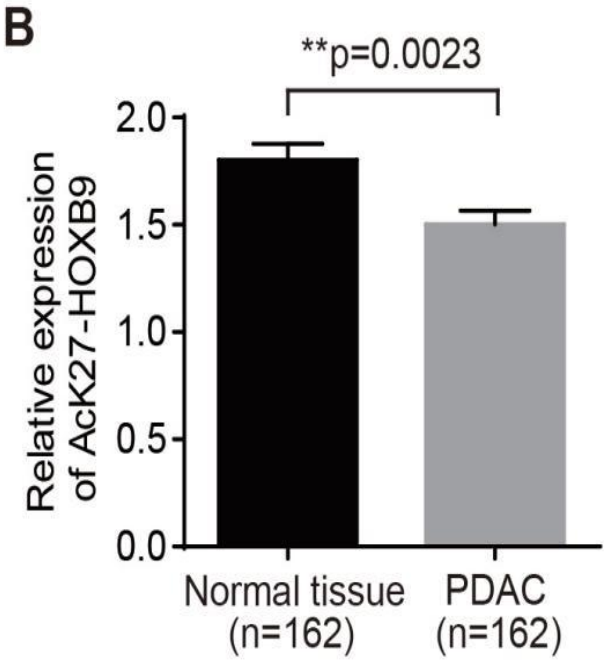
Dr. Jun Zhan

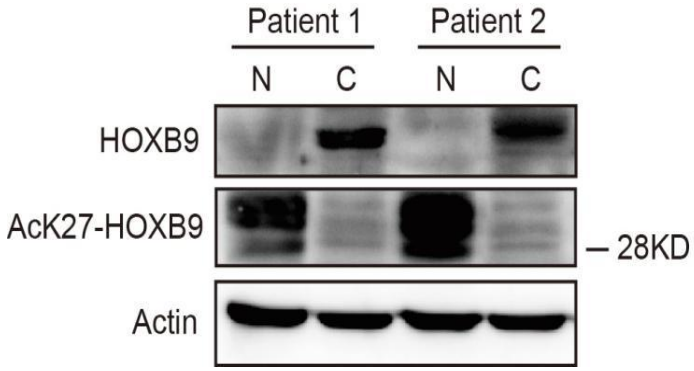
HOXB9 is upregulated in PDAC



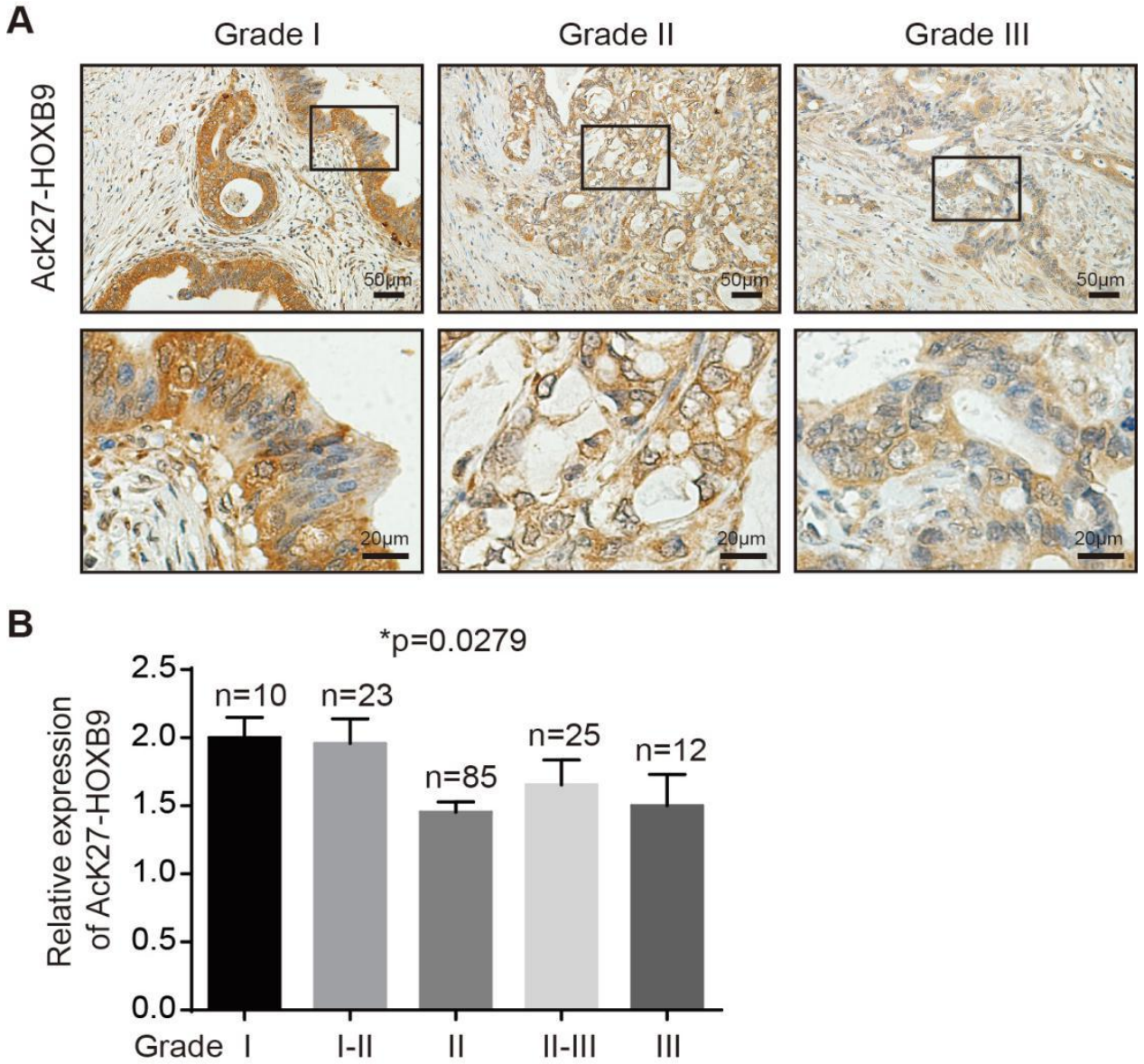
AcK27-HOXB9 is downregulated in PDAC



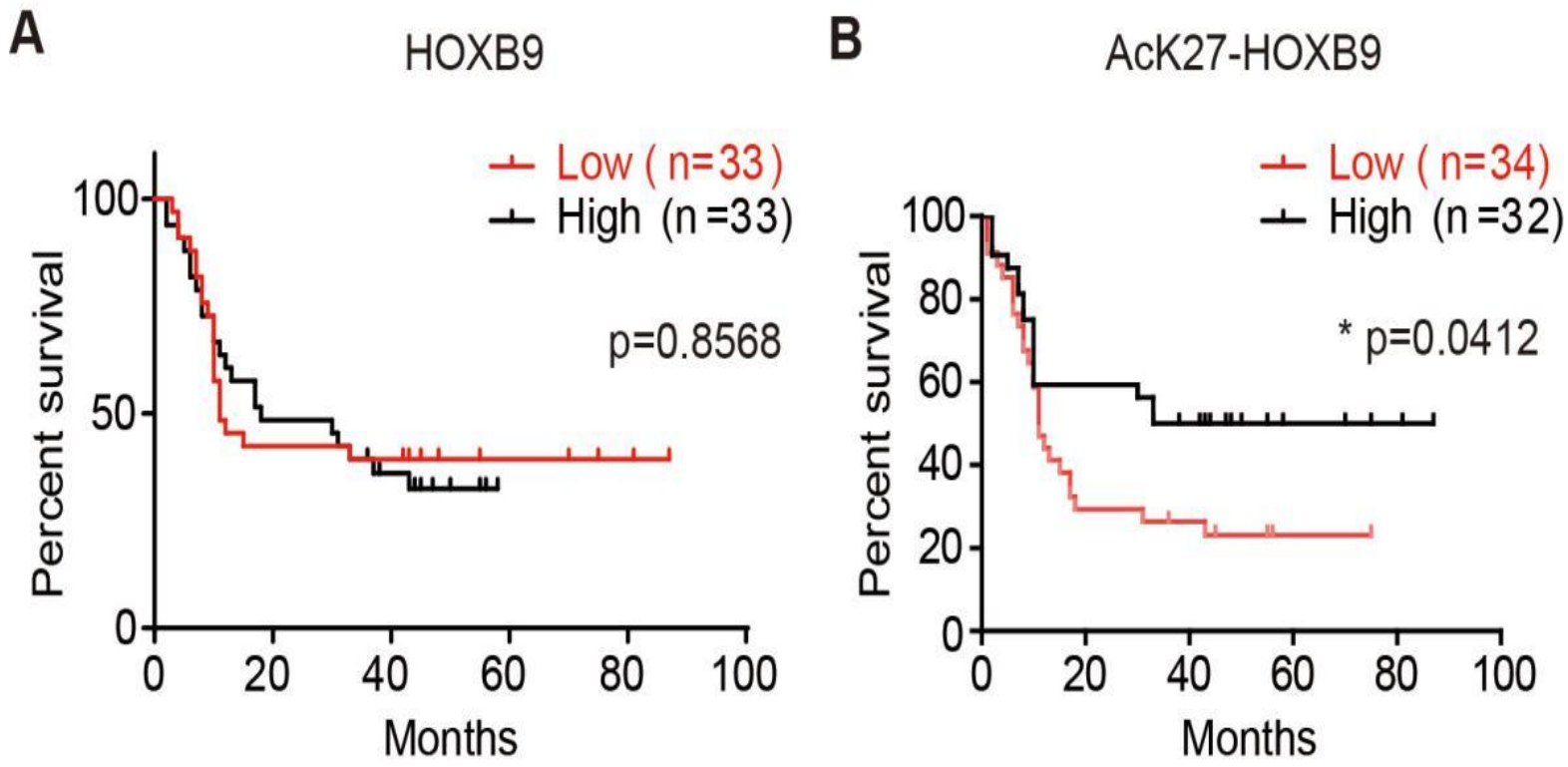




The level of AcK27-HOXB9 is correlated with PDAC progression



The level of AcK27-HOXB9 is correlated with PDAC patients prognosis



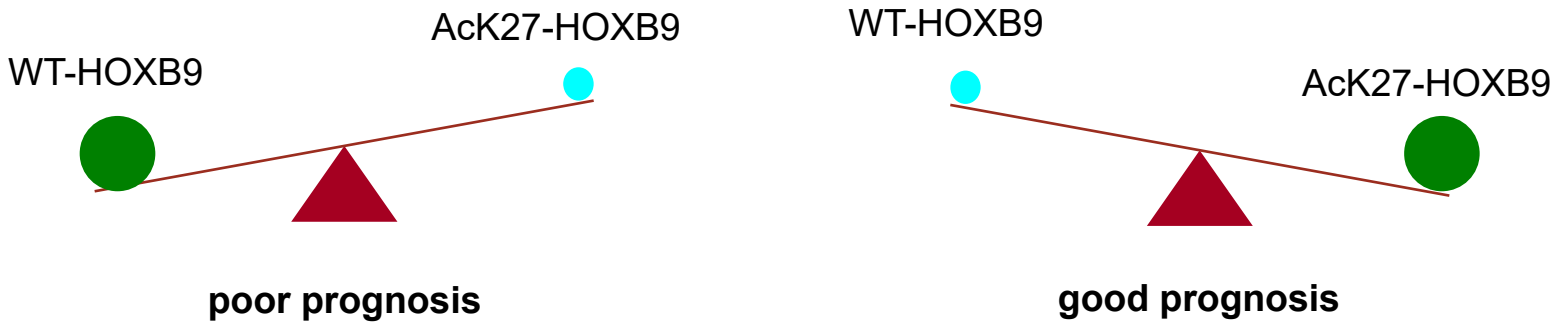
Conclusions

1. Theoretical significance:

   Expression of an mRNA is not necessarily parallel with the expression of its encoded protein; the expression of a protein is not necessarily parallel with its biological function. Post-translational modification and location of protein must be considered.

2. Clinical significance

   Wild-type HOXB9 promotes tumour progression, while AcK27-HOXB9 inhibits growth and metastasis of tumour. Ratio of wild-type/AcK27 HOXB9 may predicts the prognosis of patients.



Granted patent

证书号 第3319953号

发明专利证书

发明名称：一种转录因子HOXB9乙酰化位点的特异性抗体及其制备方法

发明人：张宏权；万军虎；战军

专利号：ZL 2016 1 0498222.X

专利申请日：2016年06月30日

专利权人：北京大学

地址：100191 北京市海淀区颐和园路5号

授权公告日：2019年04月05日 授权公告号：CN 106117355 B

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局长 申长雨

2019年04月05日

Part 3

Identification and characterization of novel protein acylations

Identification and characterization of Histone isonicotinylation

Dr. Yuhan Jiang

Background

Histone benzoylation

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-05567-w OPEN

Lysine benzoylation is a histone mark regulated by SIRT2

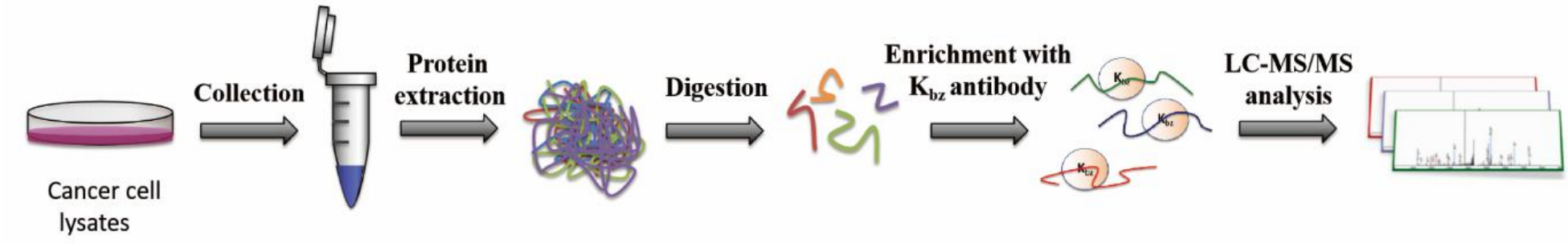
He Huang[1], Di Zhang[1], Yi Wang[2], Mathew Perez-Neut[1], Zhen Han[3], Y. George Zheng[3], Quan Hao[2] & Yingming Zhao[1]

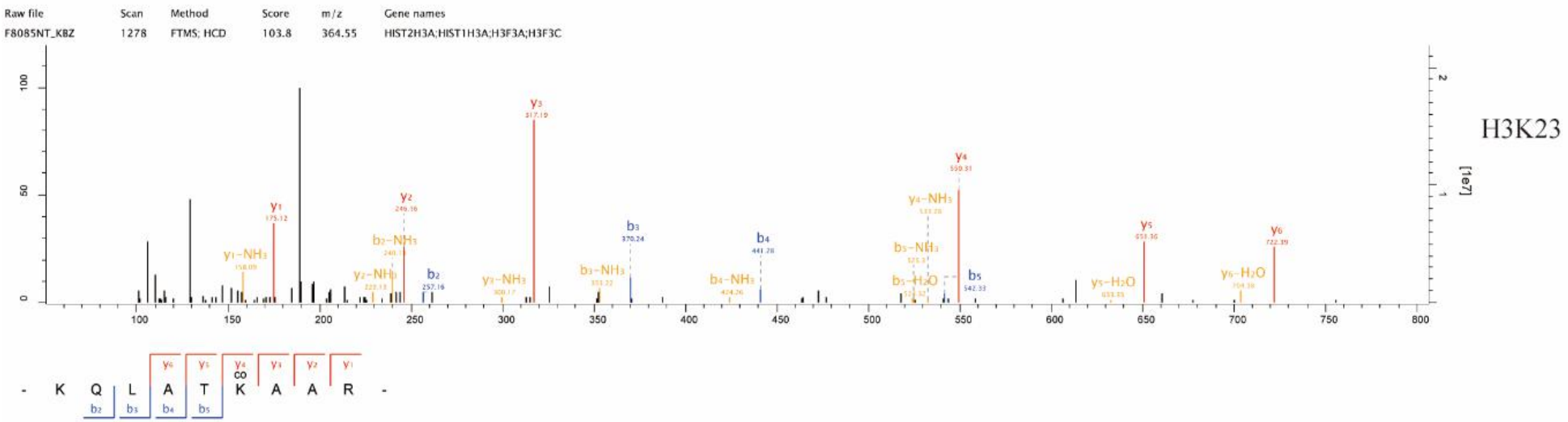
Metabolic regulation of histone marks is associated with diverse biological processes through dynamically modulating chromatin structure and functions. Here we report the identification and characterization of a histone mark, lysine benzoylation (K_{bz}). Our study identifies 22 K_{bz} sites on histones from HepG2 and RAW cells. This type of histone mark can be stimulated by sodium benzoate (SB), an FDA-approved drug and a widely used chemical food preservative, via generation of benzoyl CoA. By ChIP-seq and RNA-seq analysis, we demonstrate that histone K_{bz} marks are associated with gene expression and have physiological relevance distinct from histone acetylation. In addition, we demonstrate that SIRT2, a NAD^+-dependent protein deacetylase, removes histone K_{bz} both in vitro and in vivo. This study therefore reveals a new type of histone marks with potential physiological relevance and identifies possible non-canonical functions of a widely used chemical food preservative.

Huang H, et al. Nature Communications. 2018

Identification of isonicotinylation

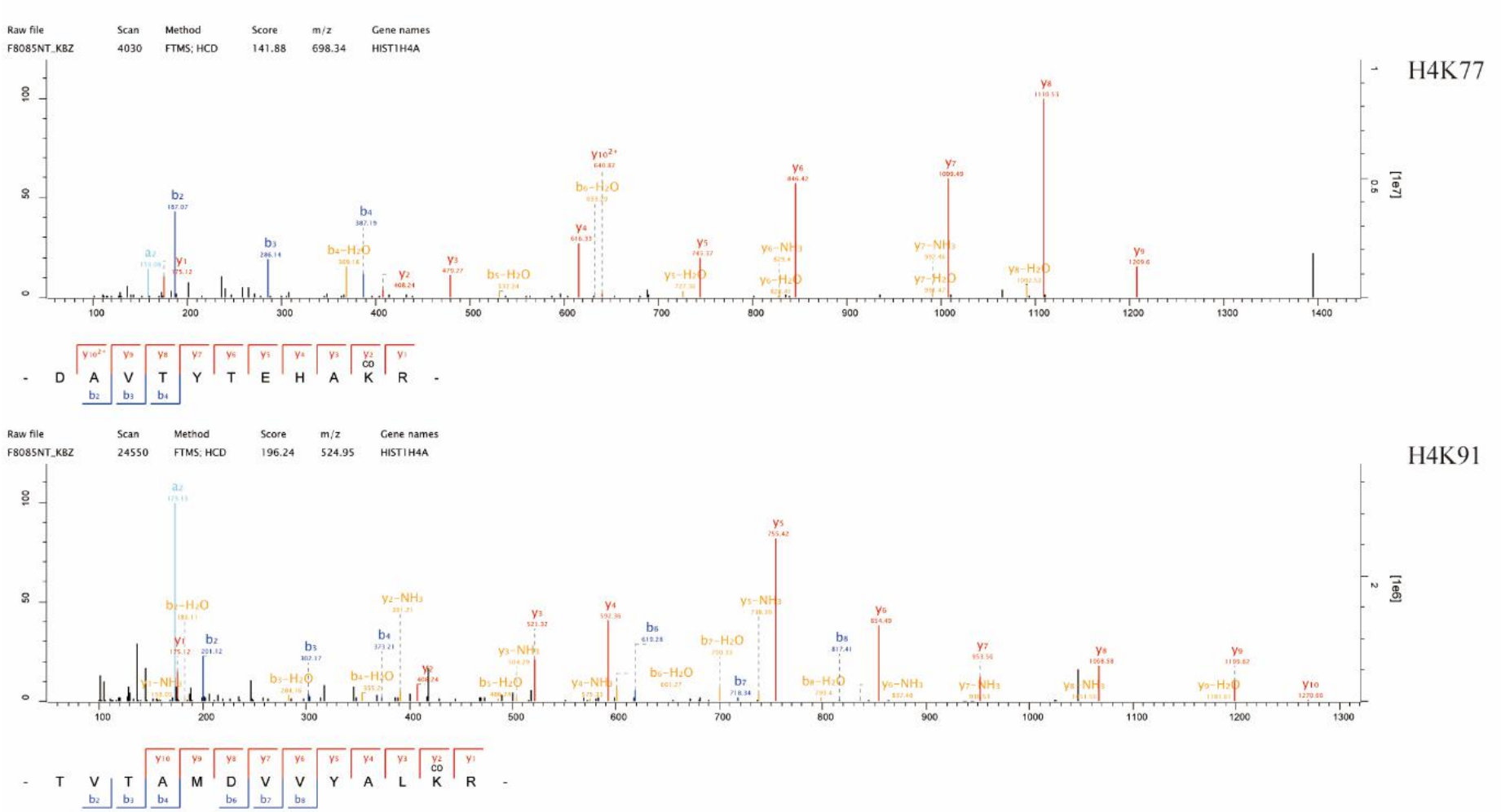
a 105.0102Da mass shift





Identification of isonicotinylation

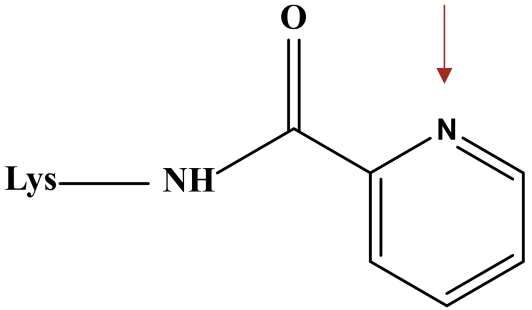
a 105.0102Da mass shift



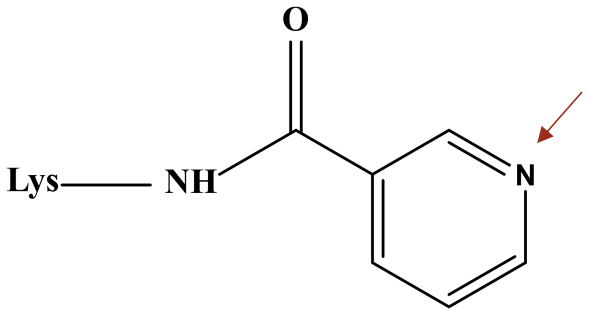
Identification of isonicotinylation

a 105.0102Da mass shift

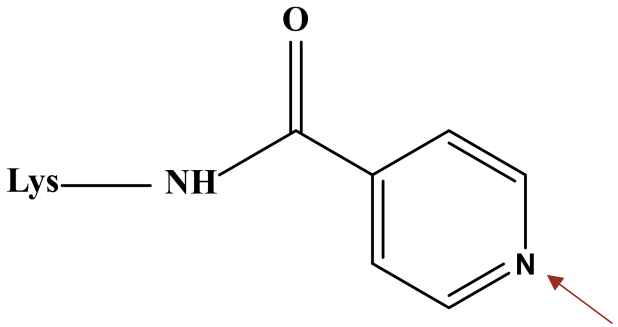
C6H4NO



Picolinylation



Nicotinylation



Isonicotinylation

Identification of isonicotinylation

Preparation of a Pan-anti-isonicotinylation

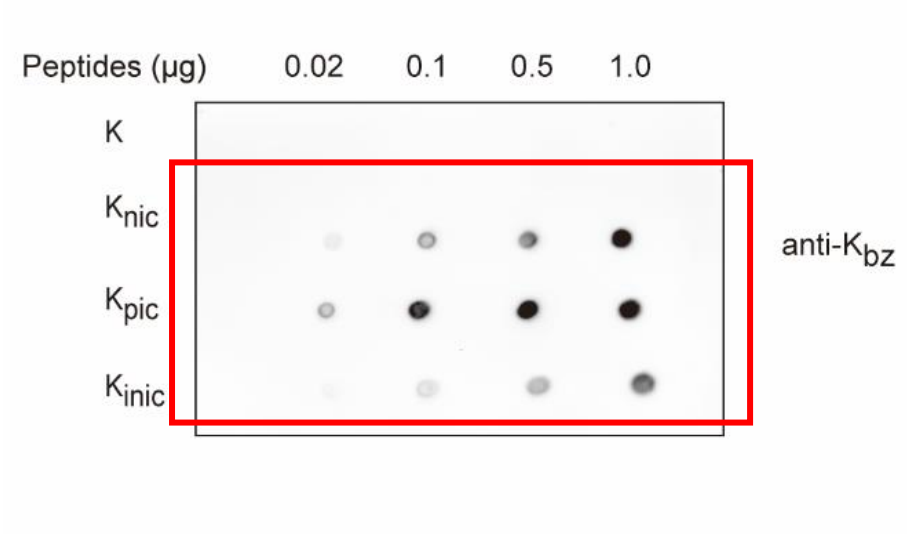
a 105.0102Da mass shift

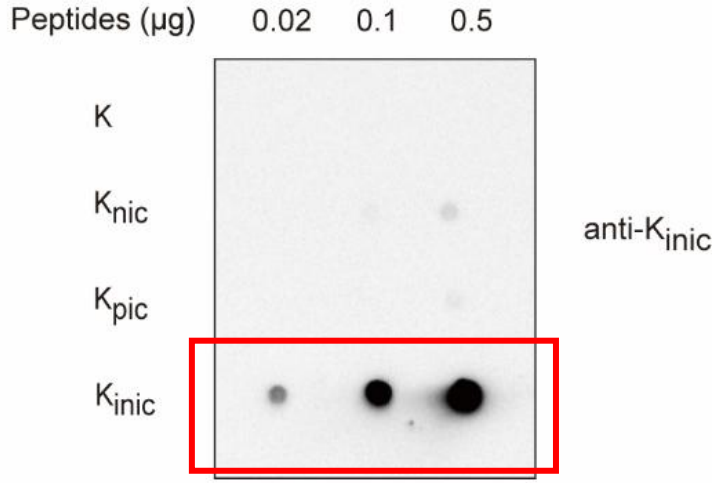
K: DAVTYTEHAKR

K_{nic}: DAVTYTEHAK_{nic}R

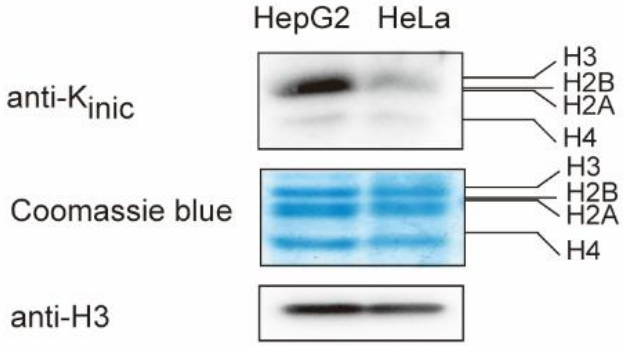
K_{pic}: DAVTYTEHAK_{pic}R

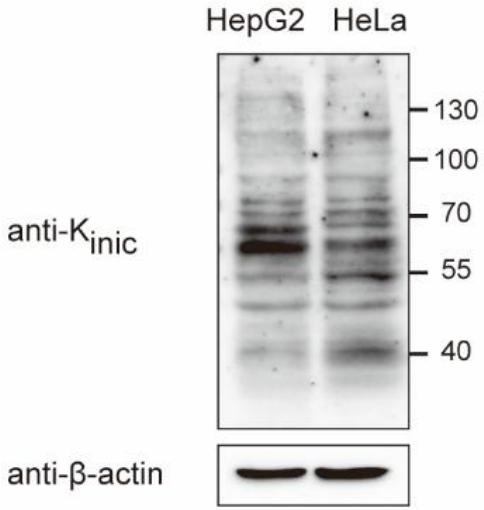
K_{inic}: DAVTYTEHAK_{inic}R

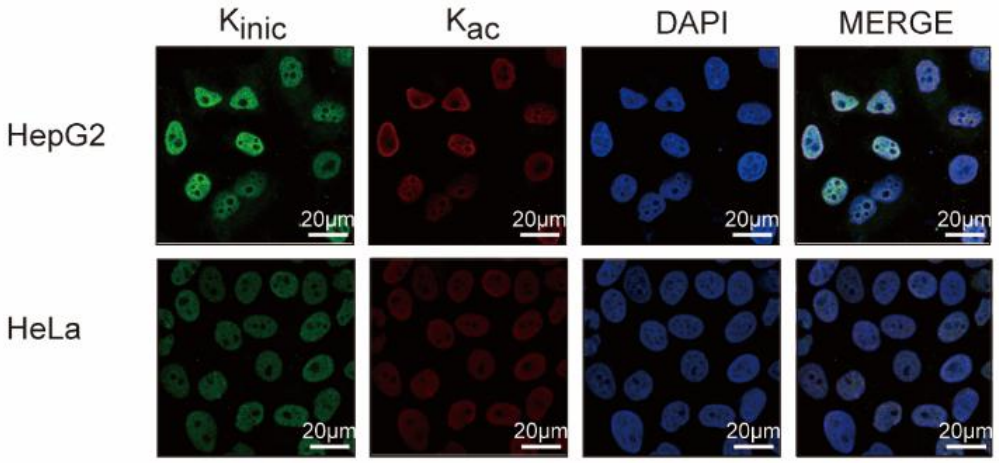




Lys is isonicotinylated in cells







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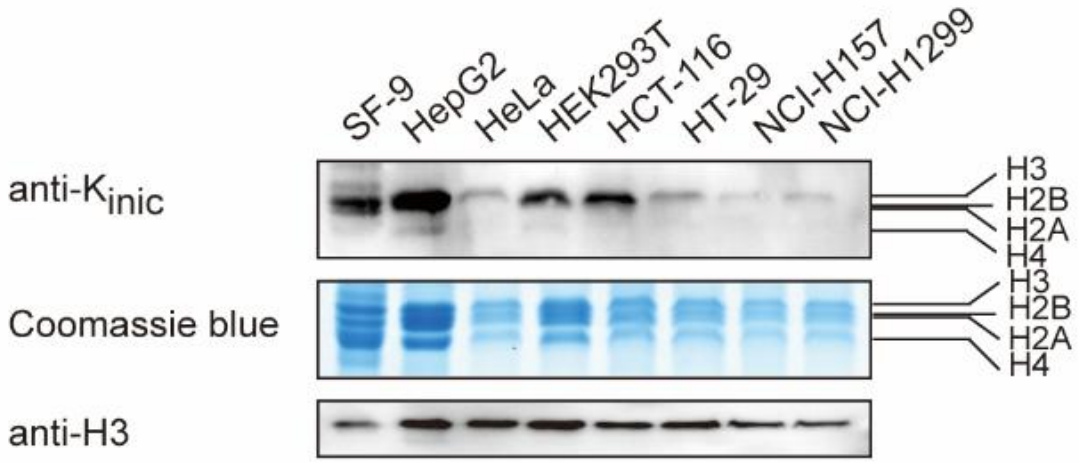
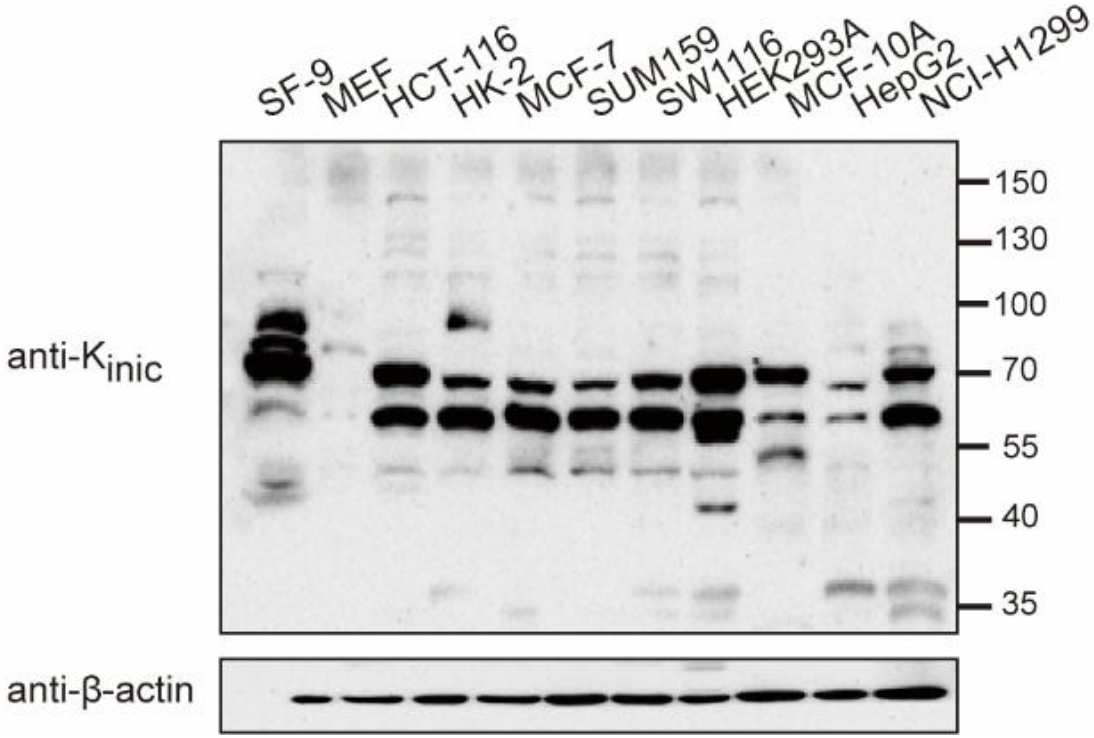
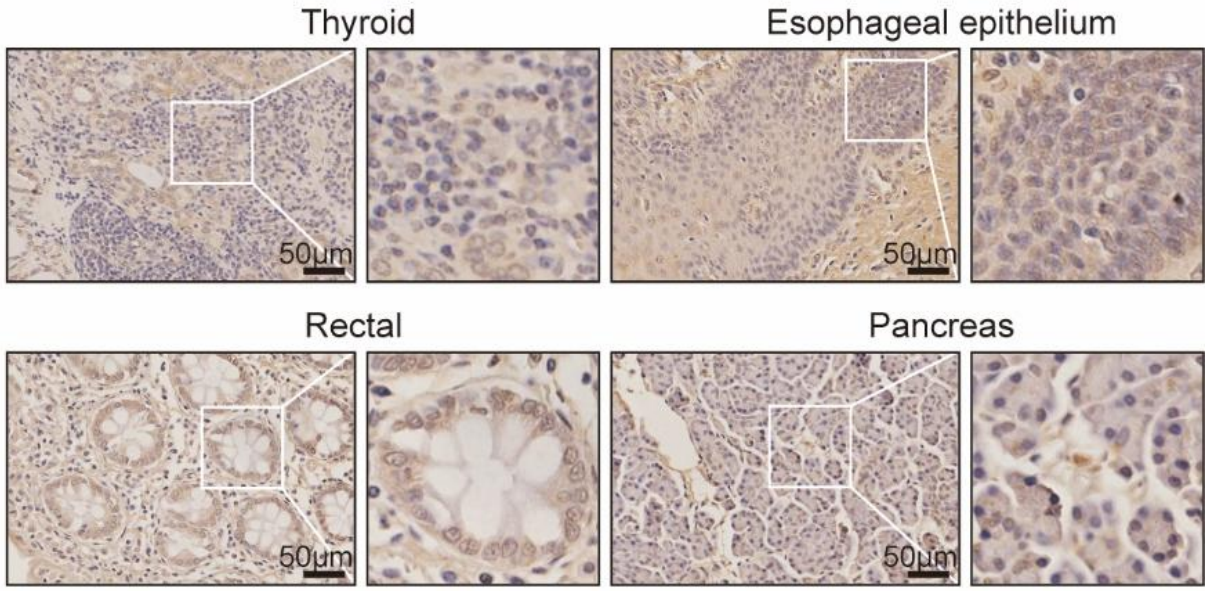
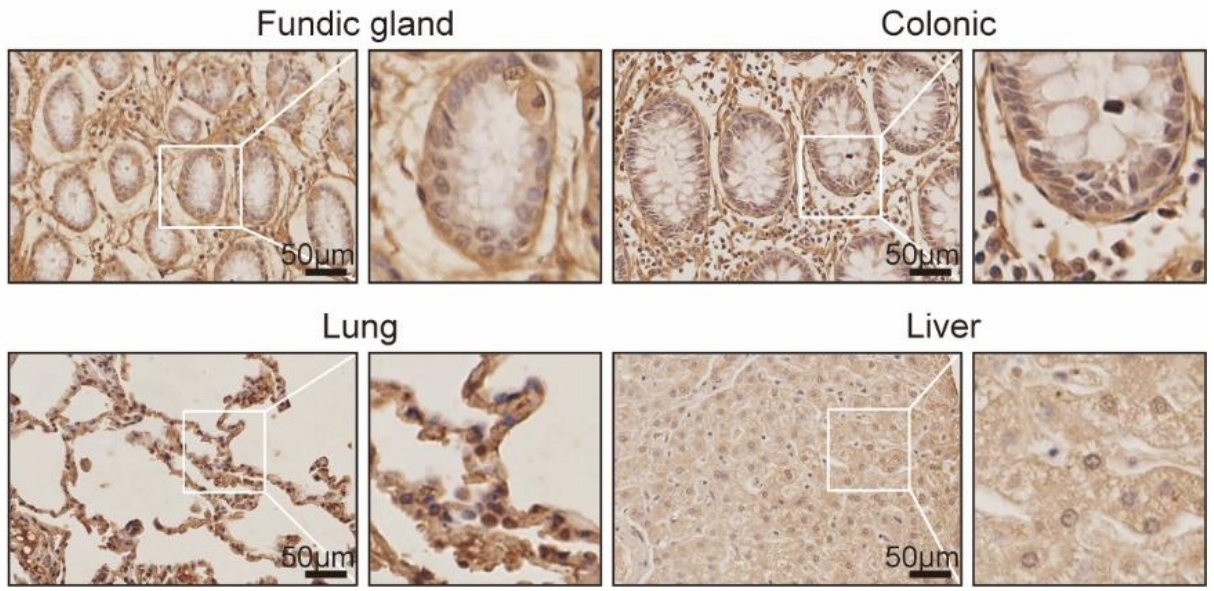


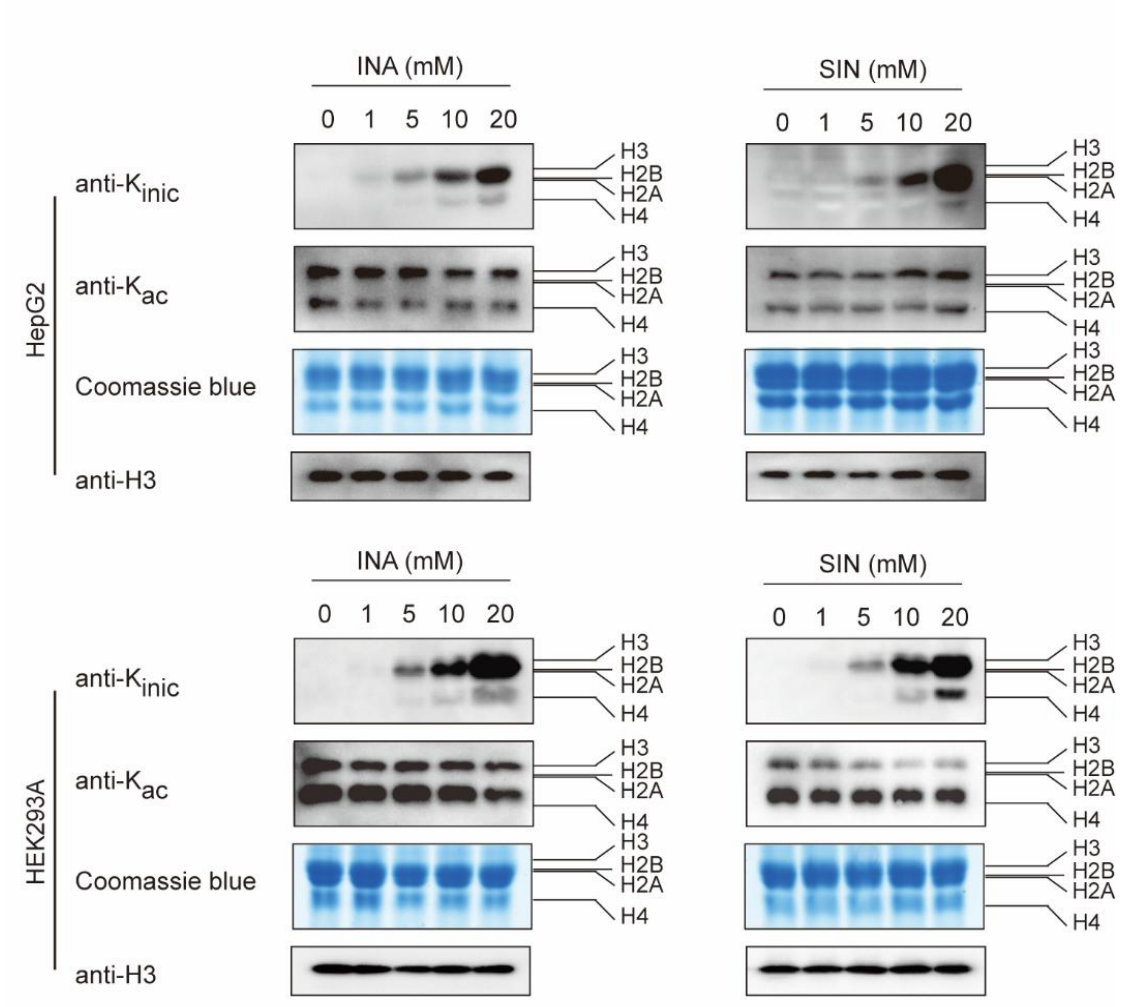


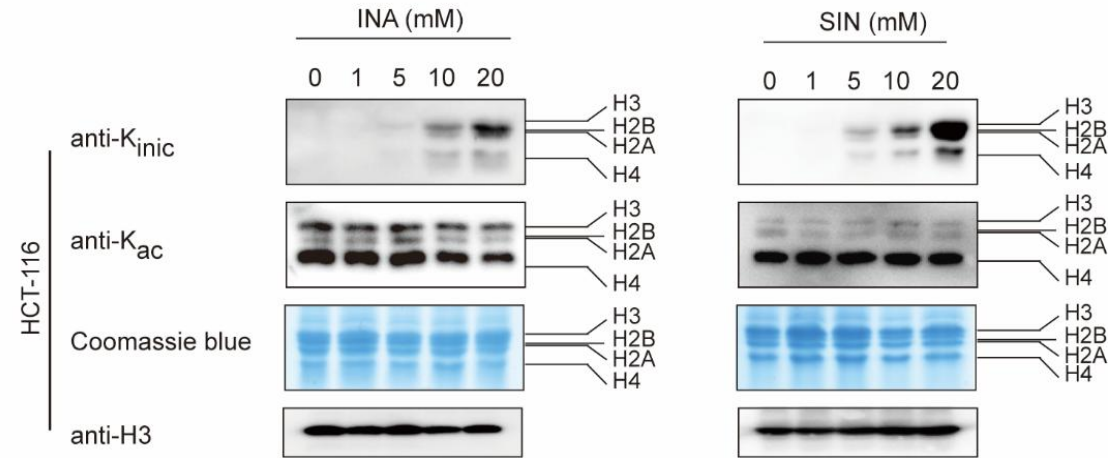
Lys is isonicotinylated in cells



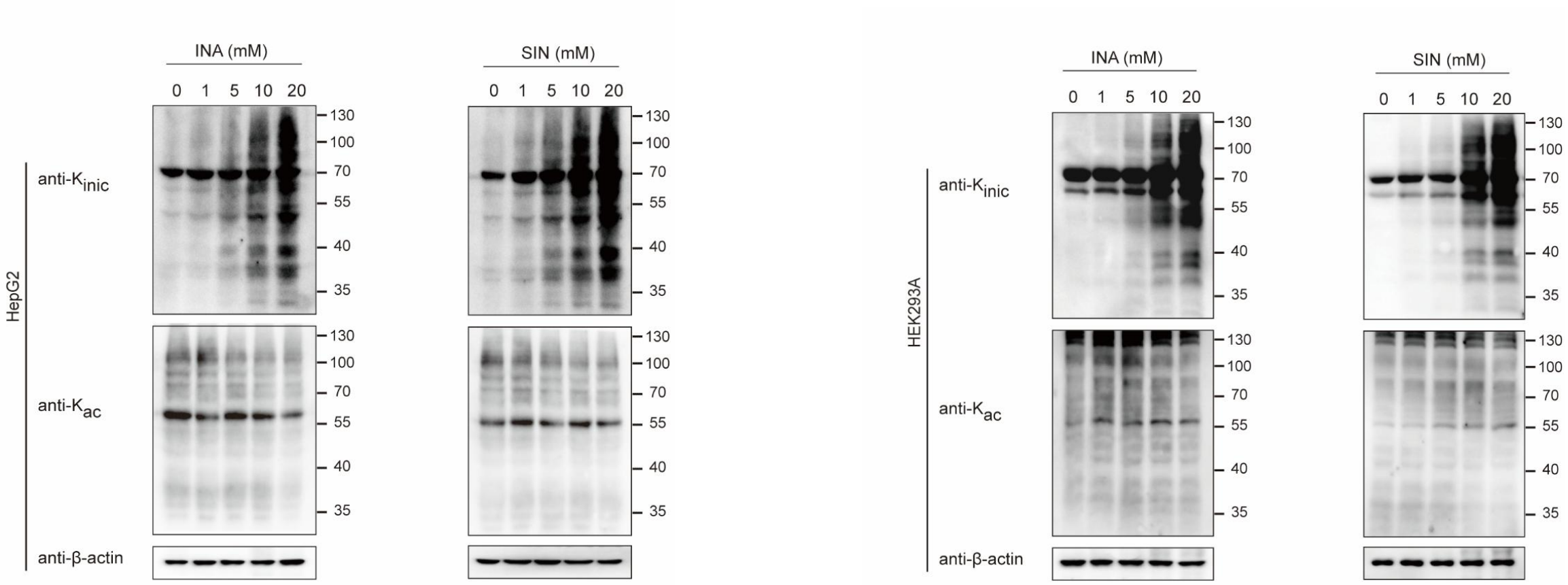


INH and SIN can induce isonicotinylation

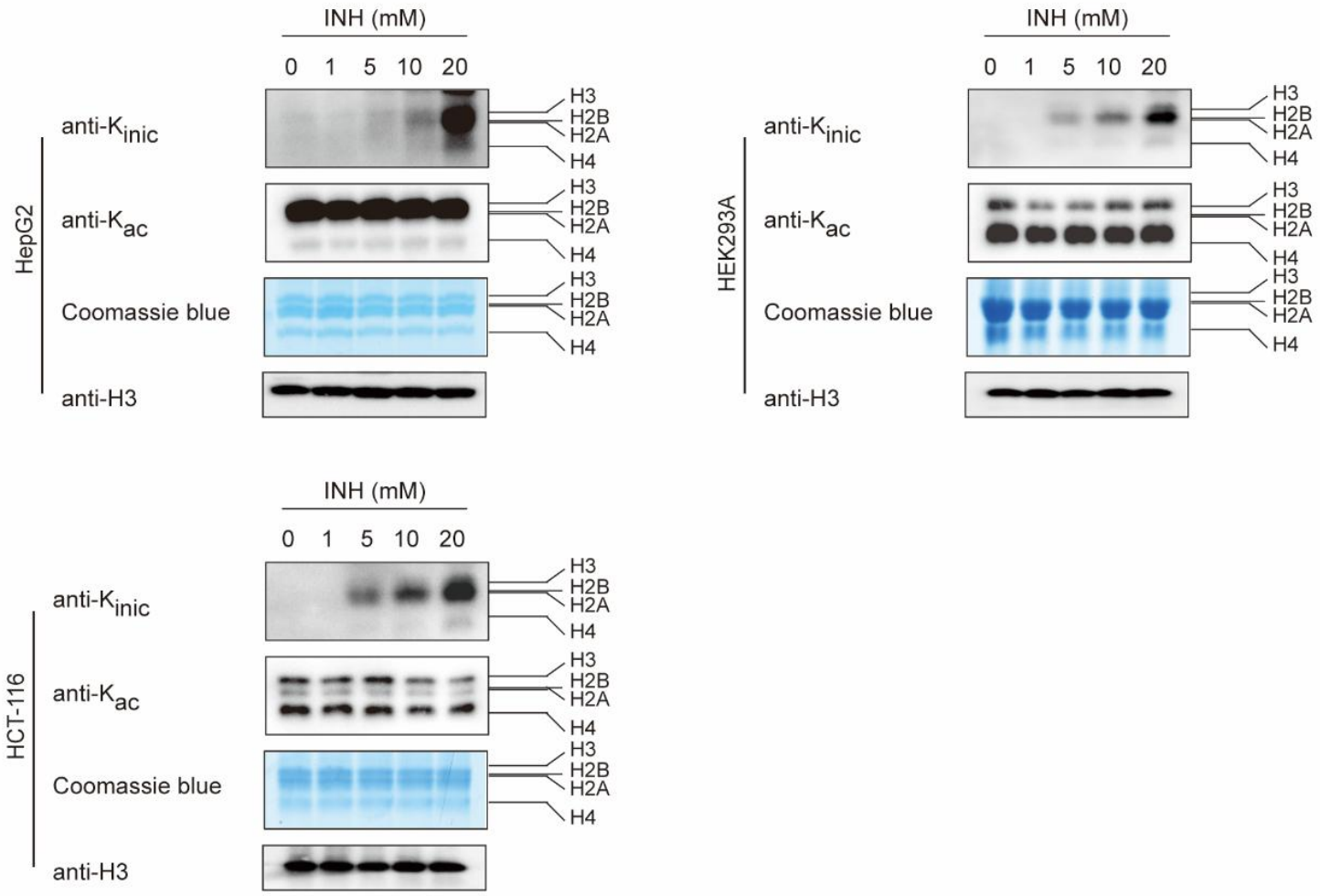




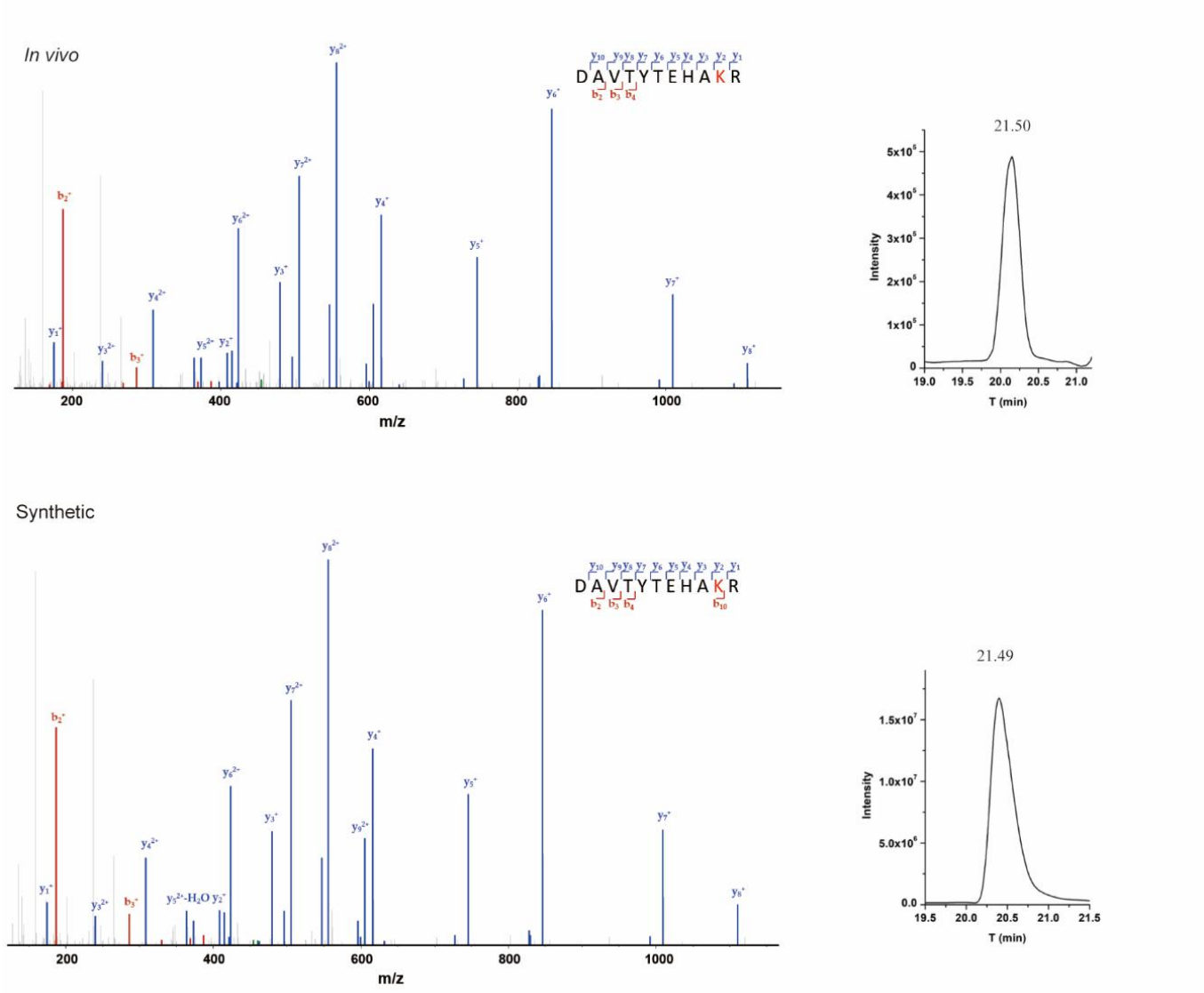
INH and SINcan induce isonicotinylation in non-histones



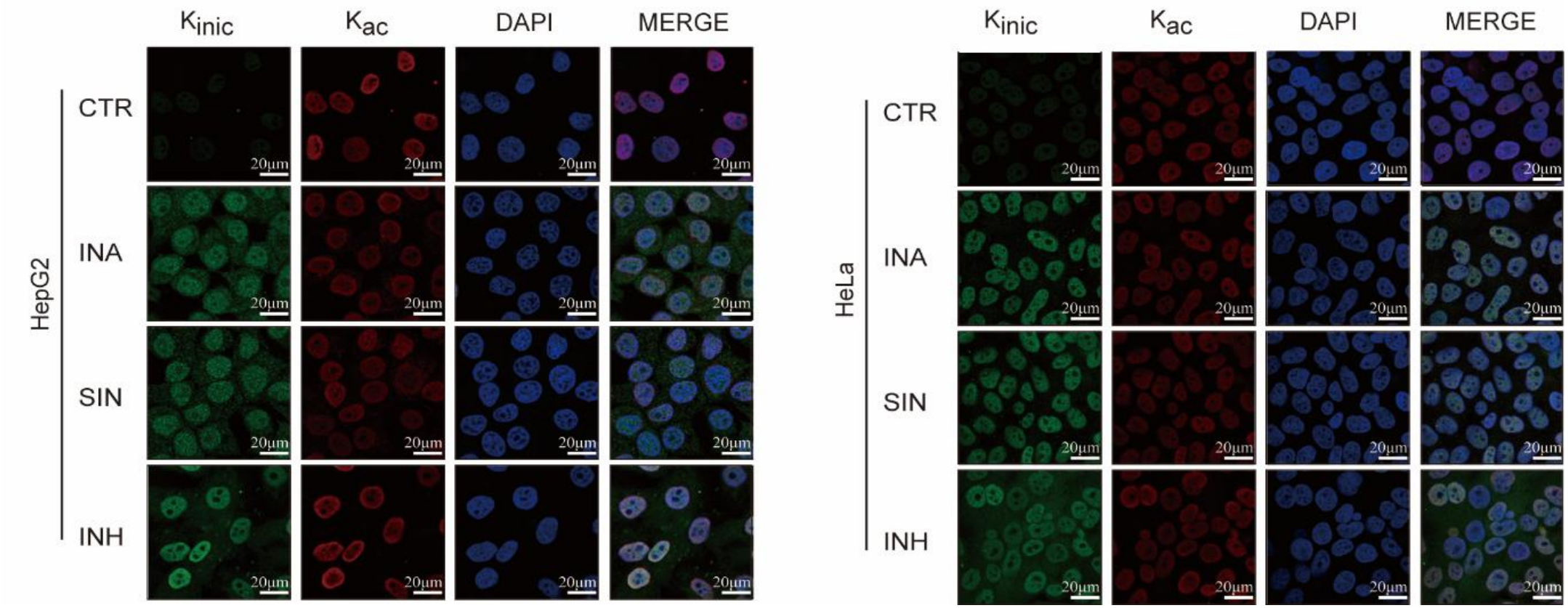
INH can induce isonicotinylation



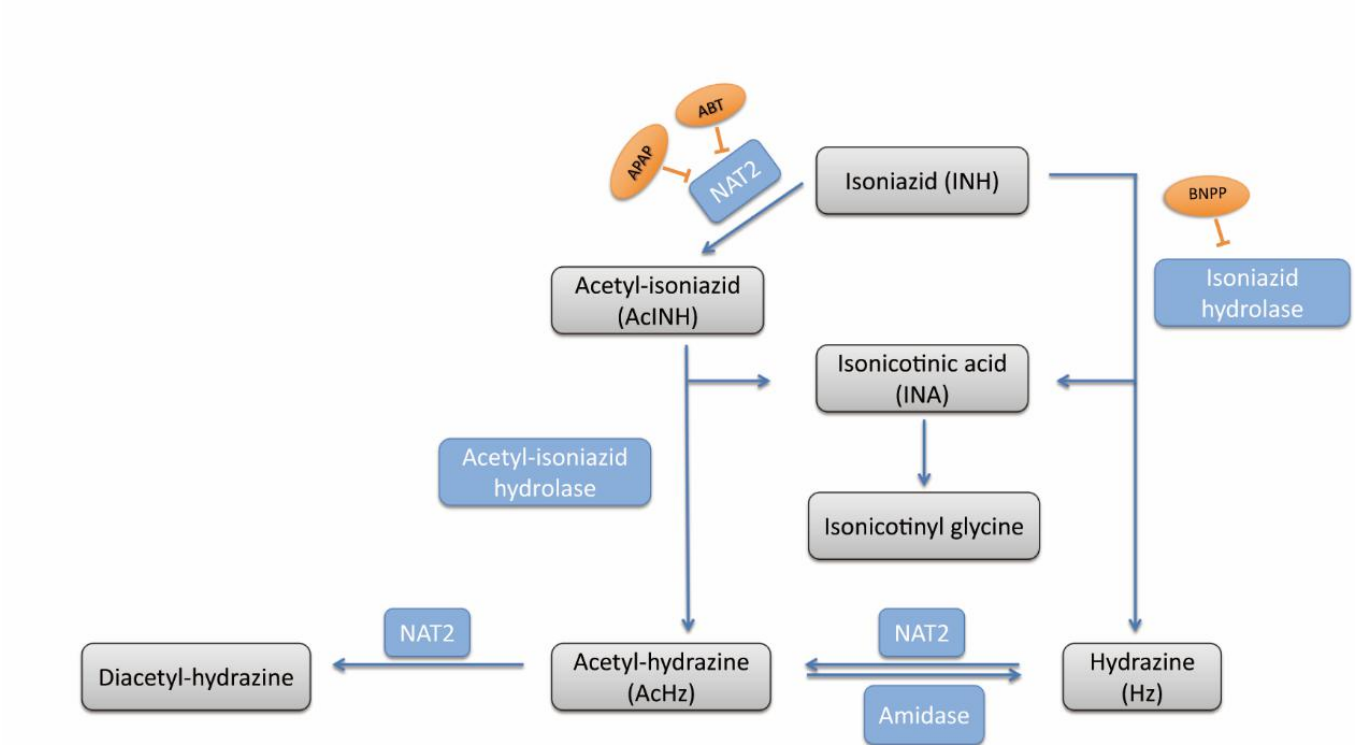
INH can induce isonicotinylation

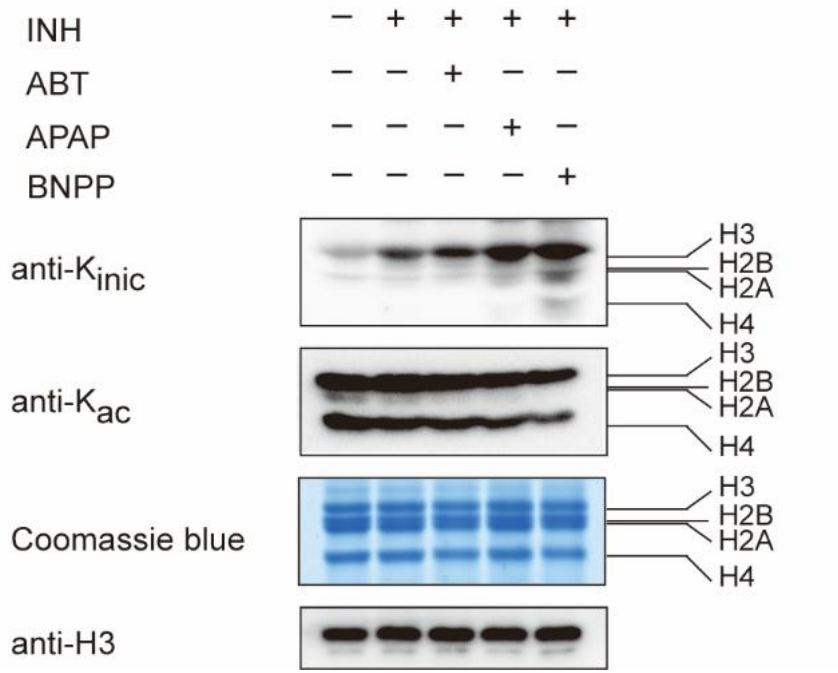


Isonicotinylation locates in the nucleus

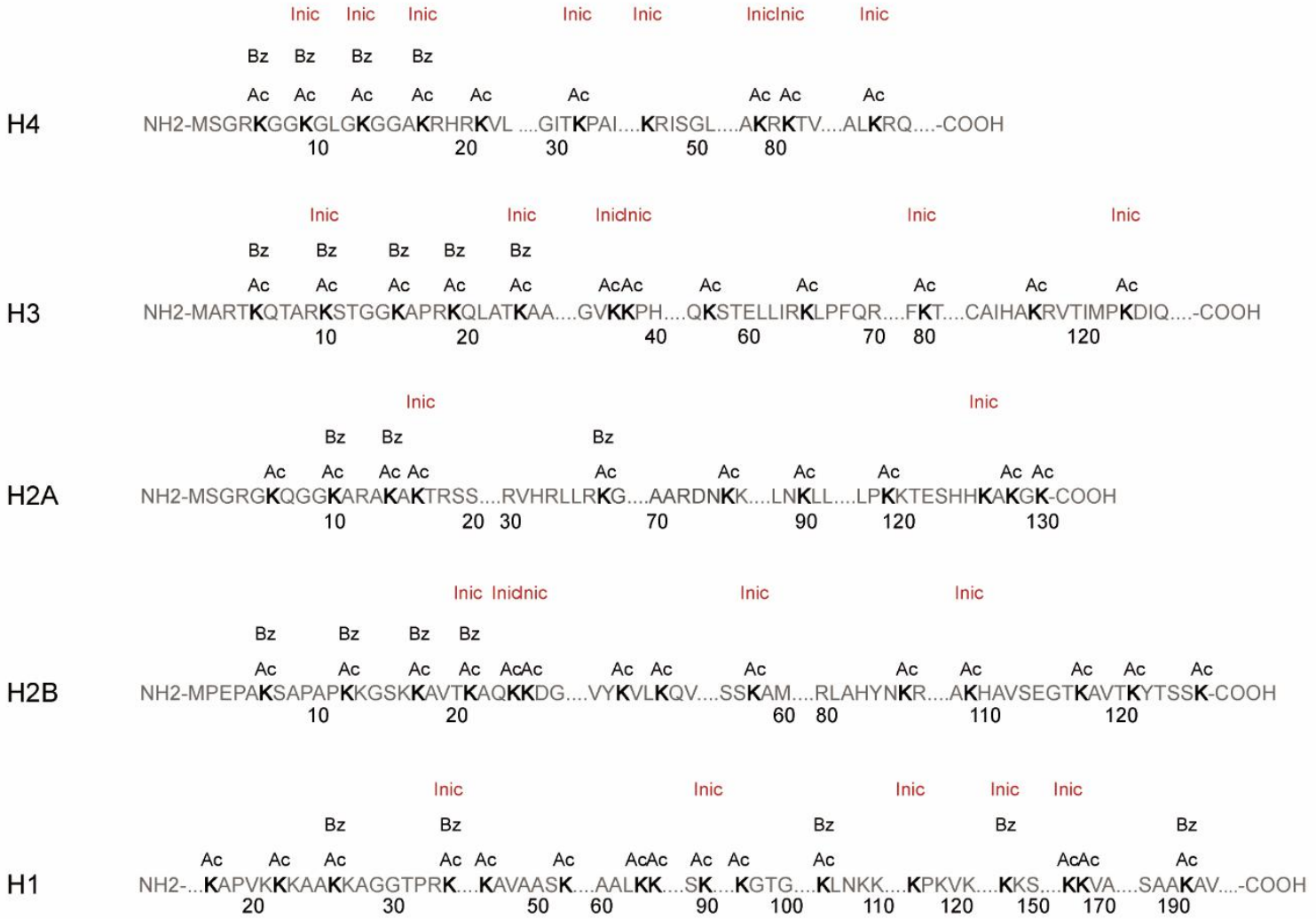


INH can directly catalyze isonicotinylation





Isonicotinylation sites in histones

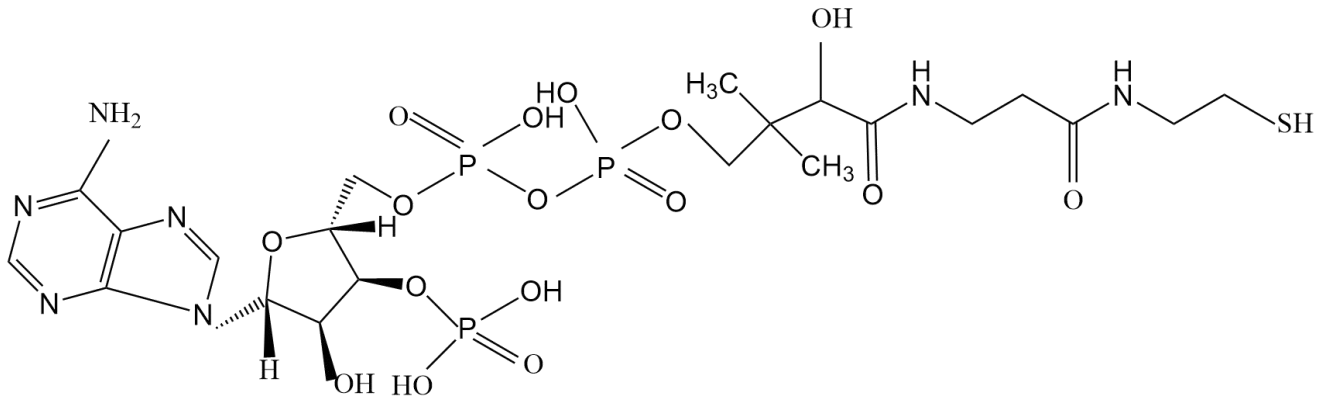


Ac: Acetylation

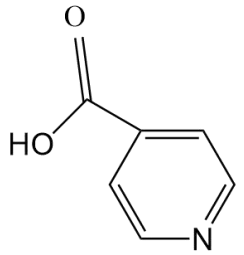
Bz: Benzoylation

Inic: Isonicotinylation

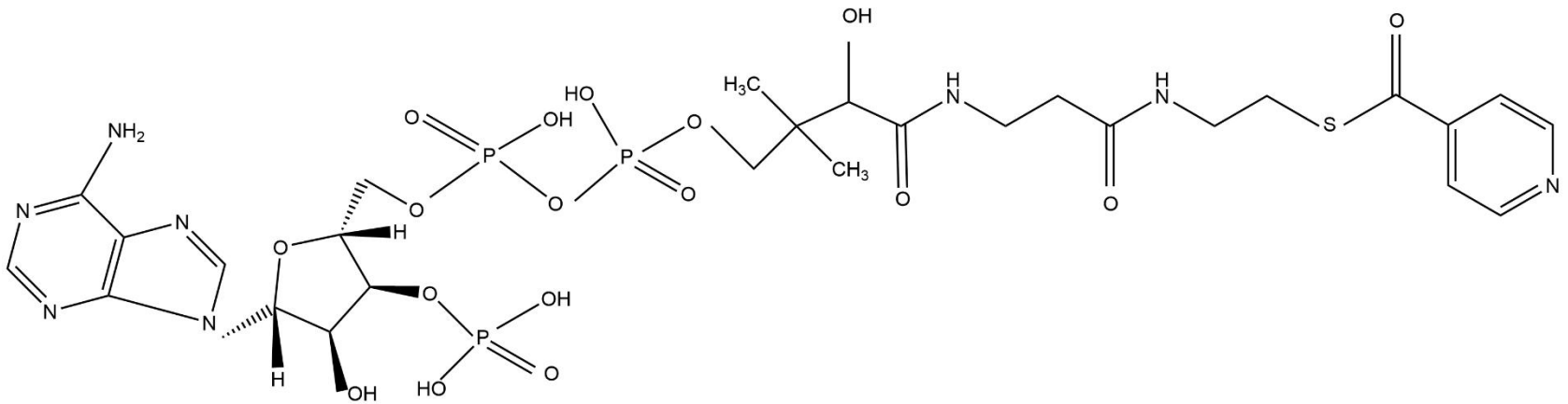
Isonicotinyl-CoA (Inic-CoA)



Coenzyme A

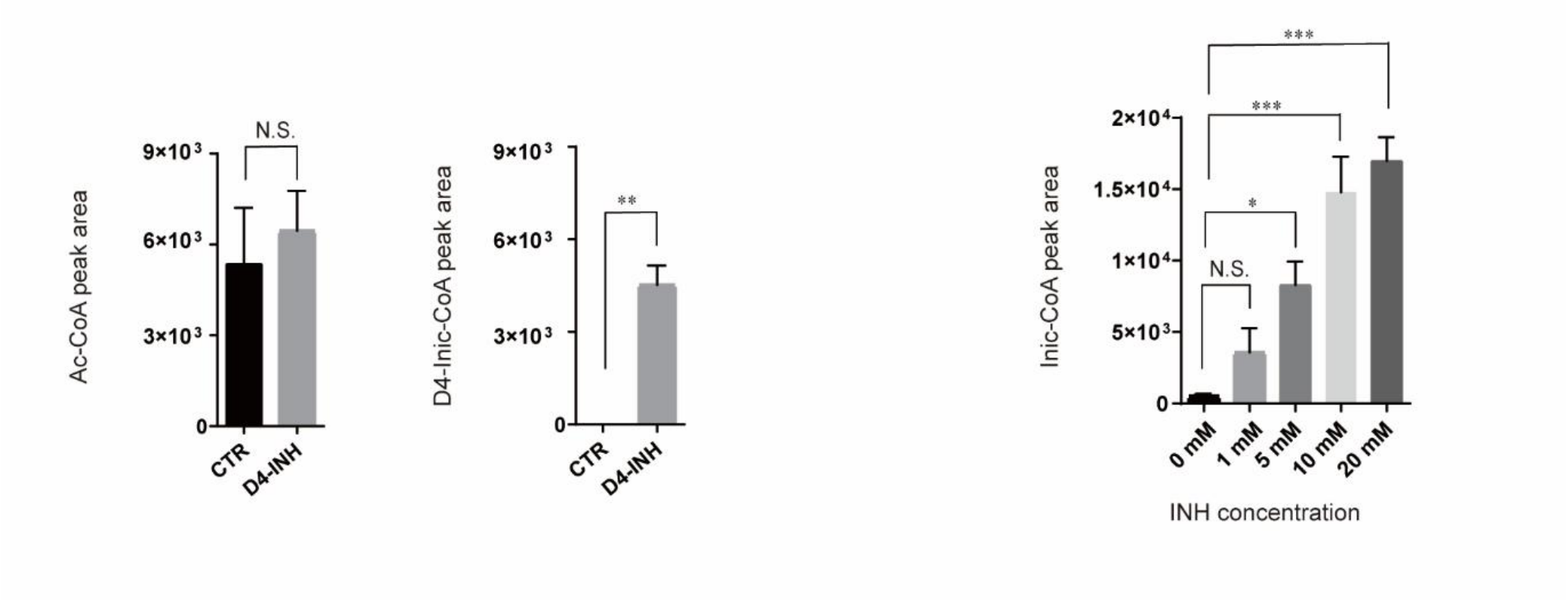


Isonicotinic acid

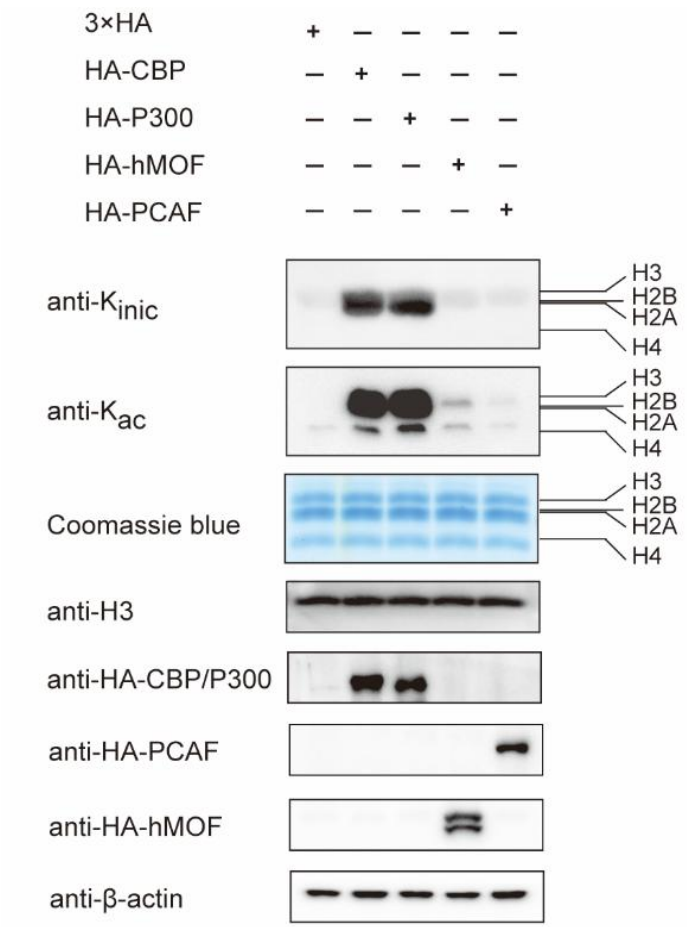


Isonicotinyl-CoA

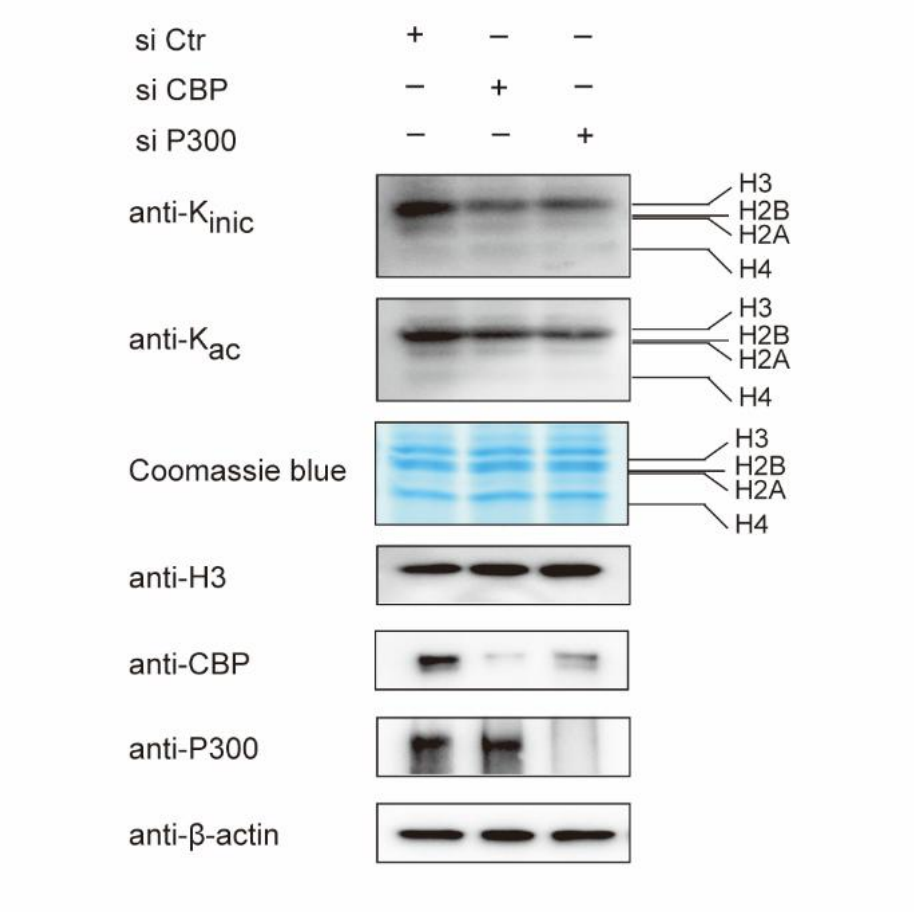
INH raises intracellular isonicotinyl-CoA

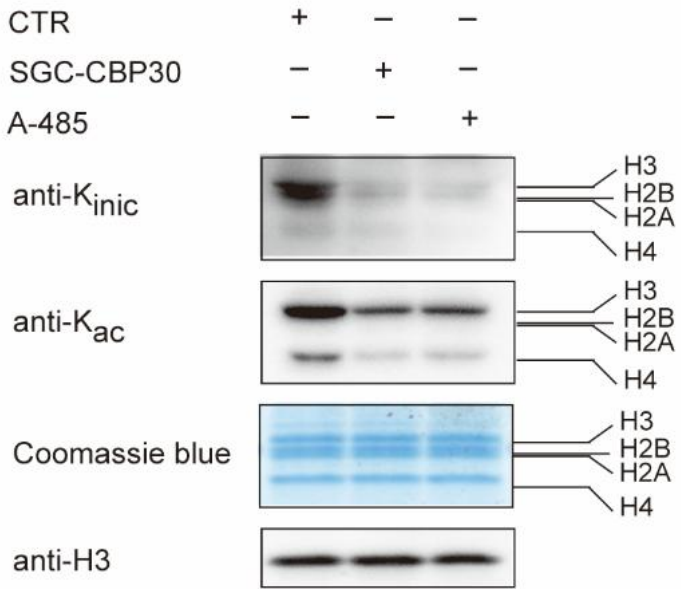


CBP/P300: isonicotinyltransferase

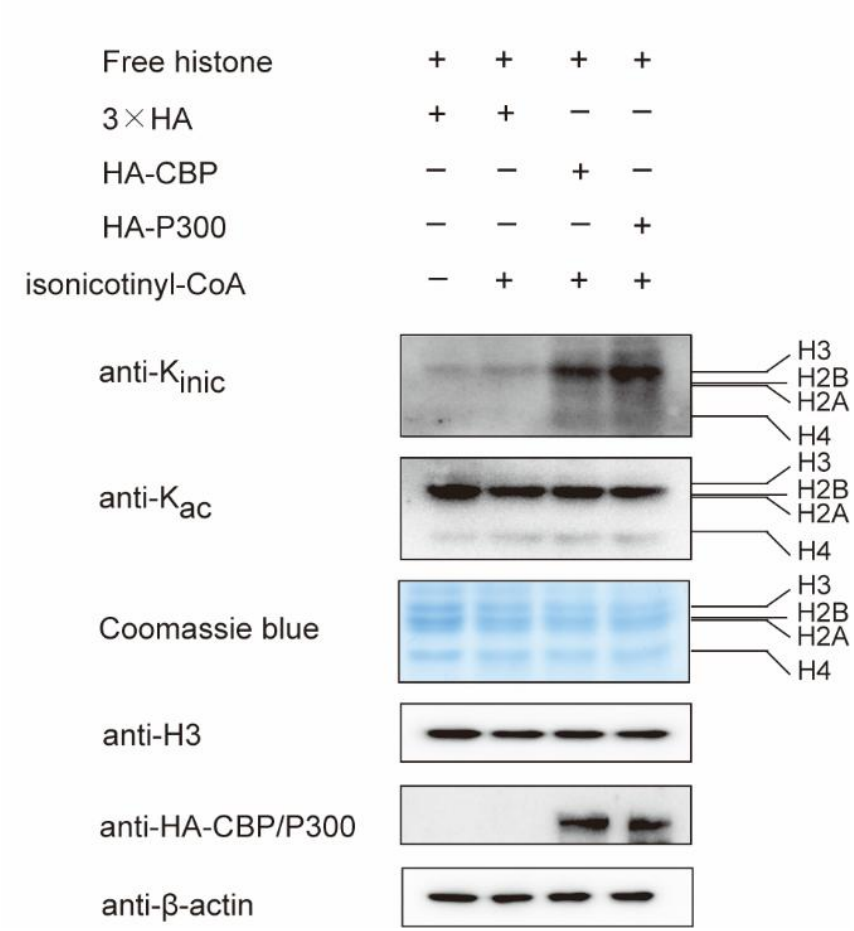


CBP/P300: isonicotinyltransferase

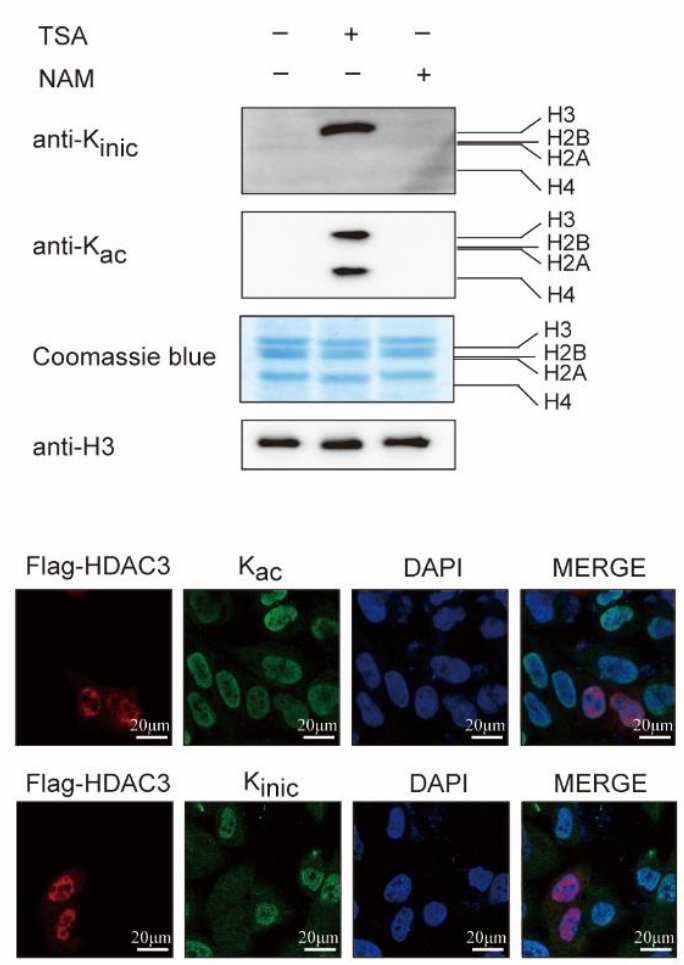


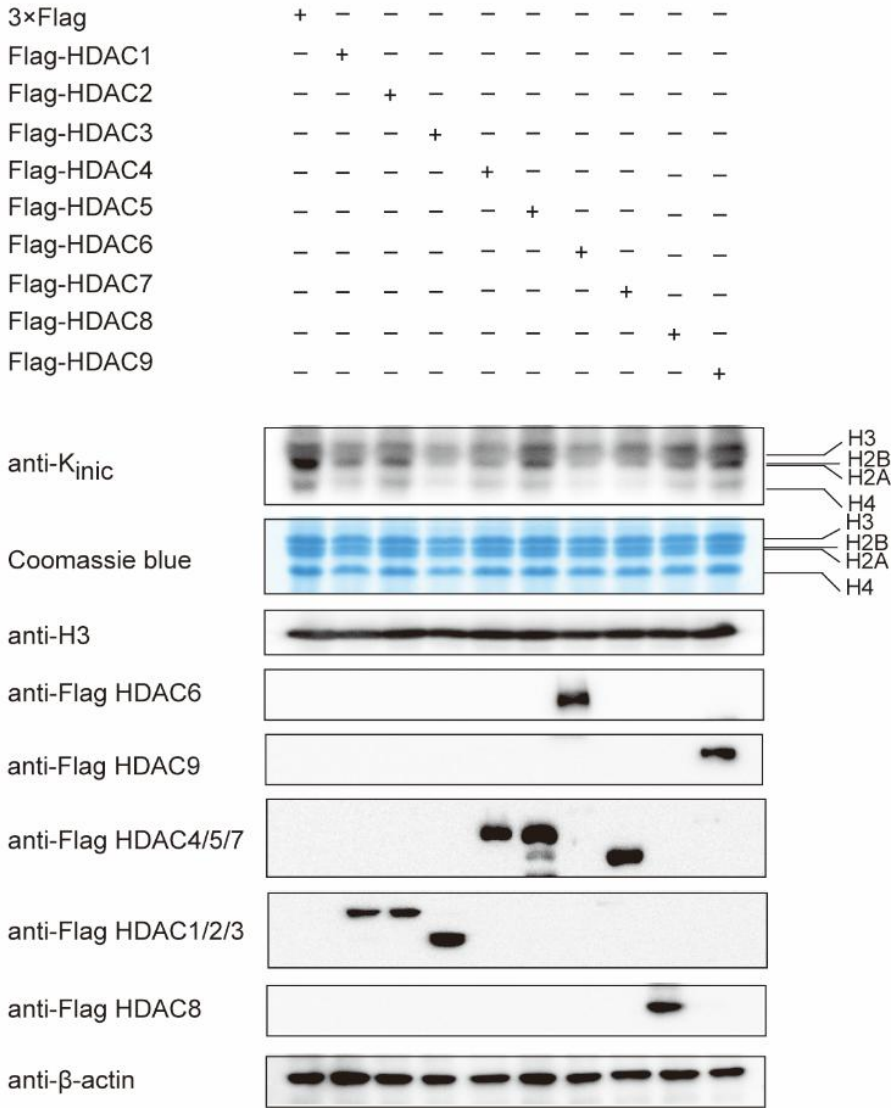


CBP/P300: isonicotinyltransferase

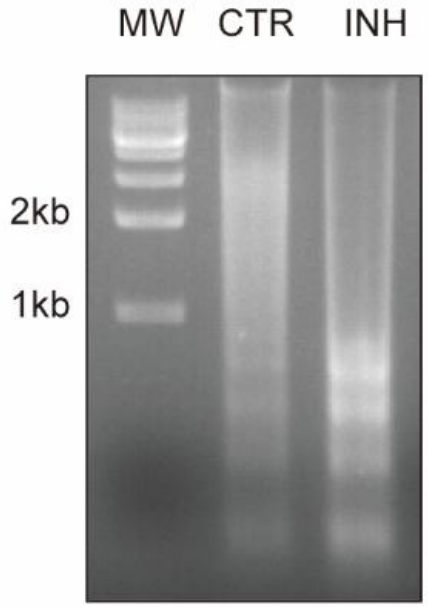


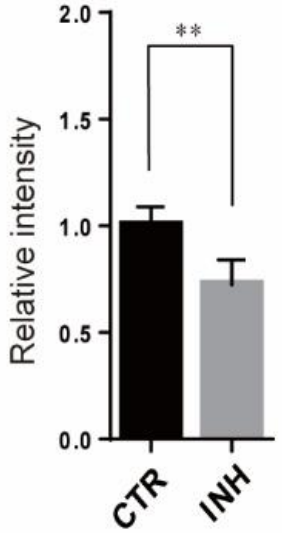
HDAC3 de-isonicotinylation

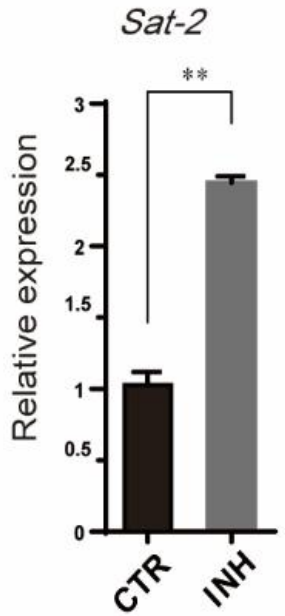




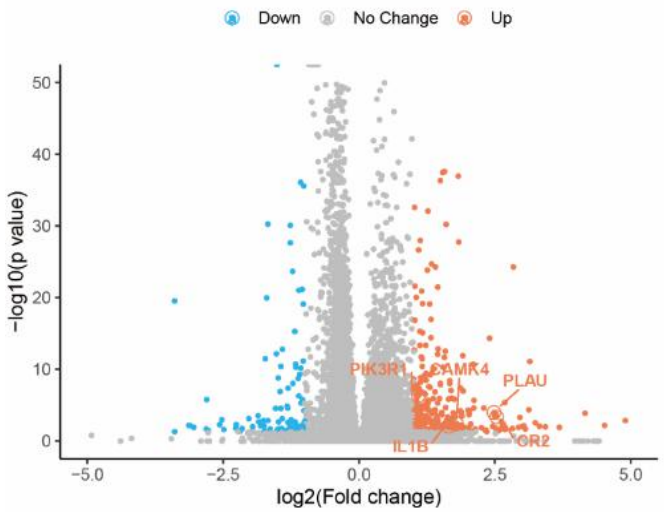
Histone isonicotinylation loosens chromatin

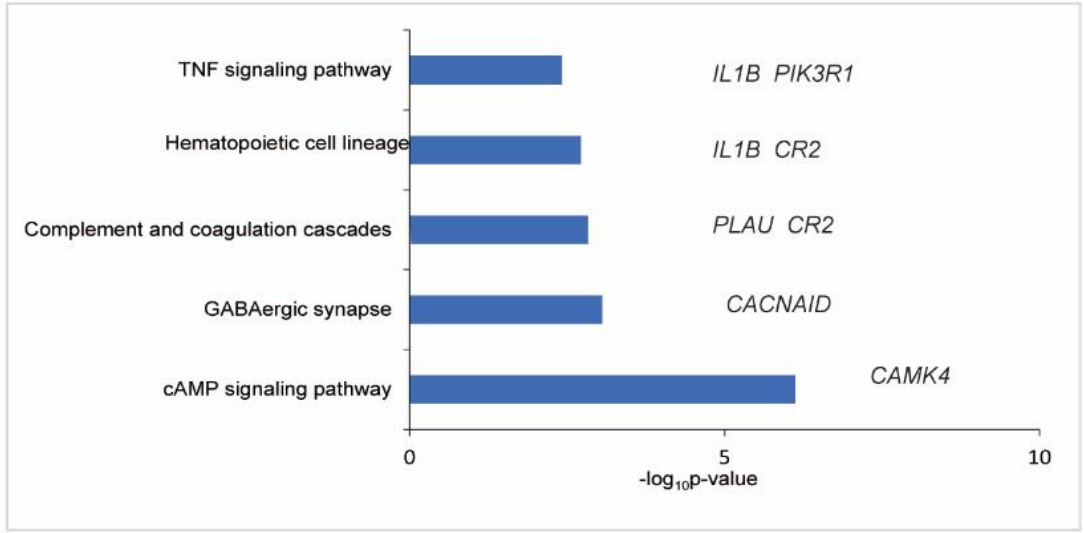


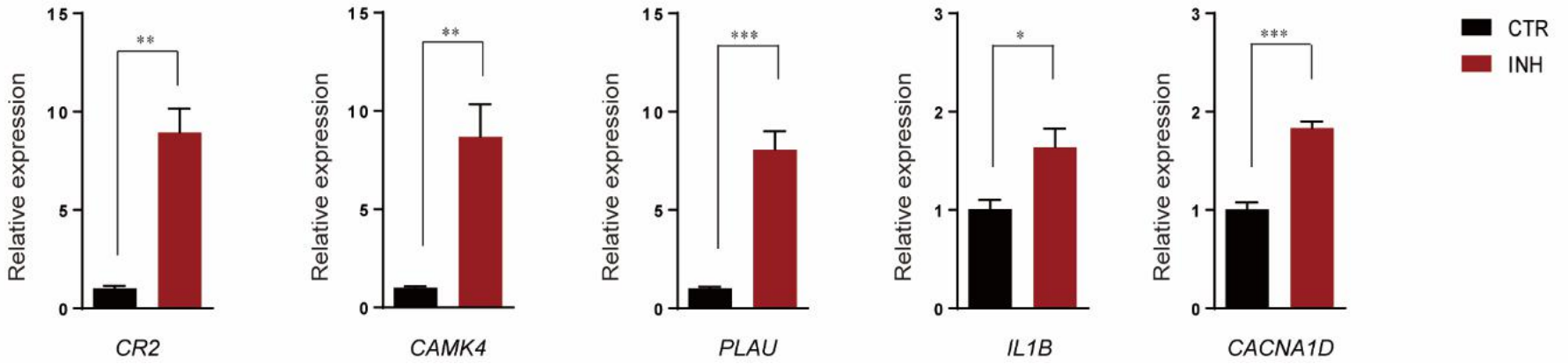




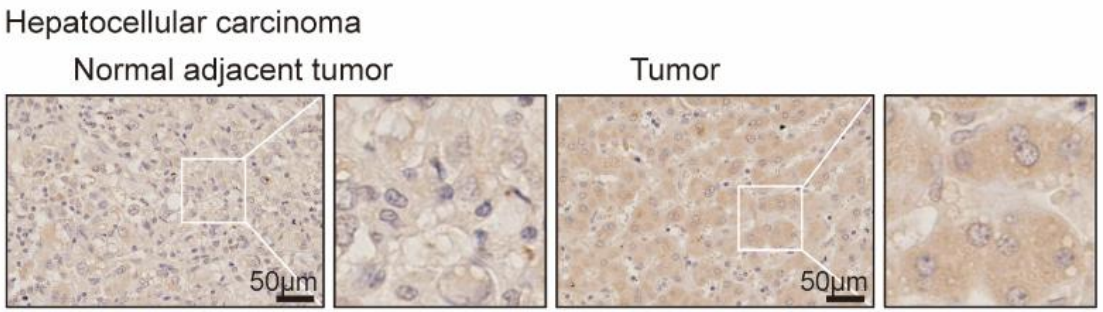
Histone isonicotinylation regulates gene expression







Histone isonicotinylation activates PI3K/Akt/mTOR



Ai et al. Biol Res (2018) 51:52
https://doi.org/10.1186/s40659-018-0202-7

Biological Research

He et al. Journal of Experimental & Clinical Cancer Research (2017) 36:175
DOI 10.1186/s13046-017-0646-6

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

FOXA1 inhibits hepatocellular carcinoma progression by suppressing PIK3R1 expression in male patients

Shujiao He[1,2], Junyi Zhang[1,2], Wan Zhang[1,2], Fengsheng Chen[1,2*] and Rongcheng Luo[1,2*]

Abstract

Background: Forkhead box A1 (FOXA1) expression is associated with various types of tumors; however, the function and underlying mechanism of FOXA1 in the development of hepatocellular carcinoma (HCC) remains obscure.

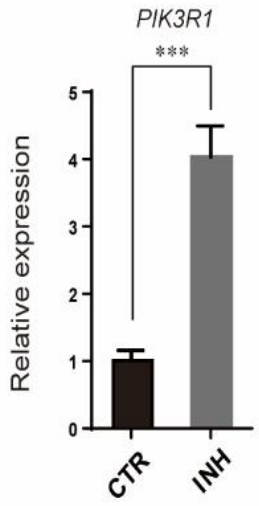
Methods: Here, we investigated the role of FOXA1 in the development of HCC by applying gene function gain and loss analysis to HepG2 and Hep3B cell lines, and comparing outcomes with those of clinical HCC samples.

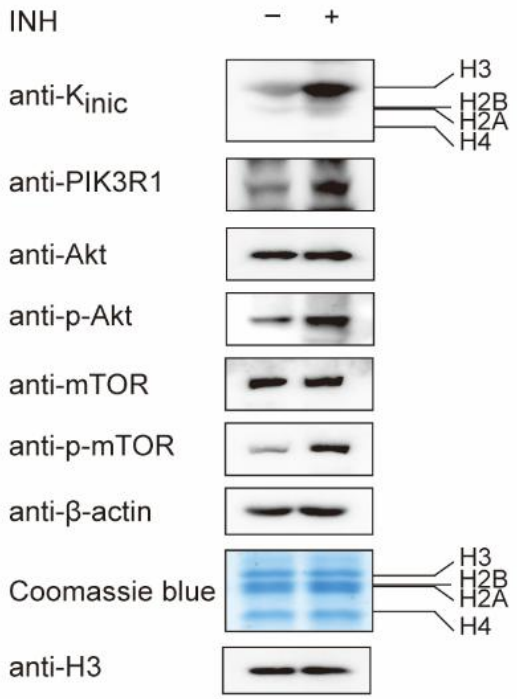
Results: Phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1), which encodes protein PI3Kp85 (p85), was identified as a FOXA1 target gene. Analyses of the mechanism and function revealed that FOXA1 suppresses hepatocellular carcinoma cell viability and motility by inhibiting PI3K/Akt signaling through direct inhibition of PIK3R1 transcription. Moreover, in clinical samples from male HCC patients, FOXA1 expression was much lower, whereas PI3Kp85 levels were much higher in tumor than in non-tumor tissues. Elevated PI3Kp85 is an unfavorable factor in HCC.

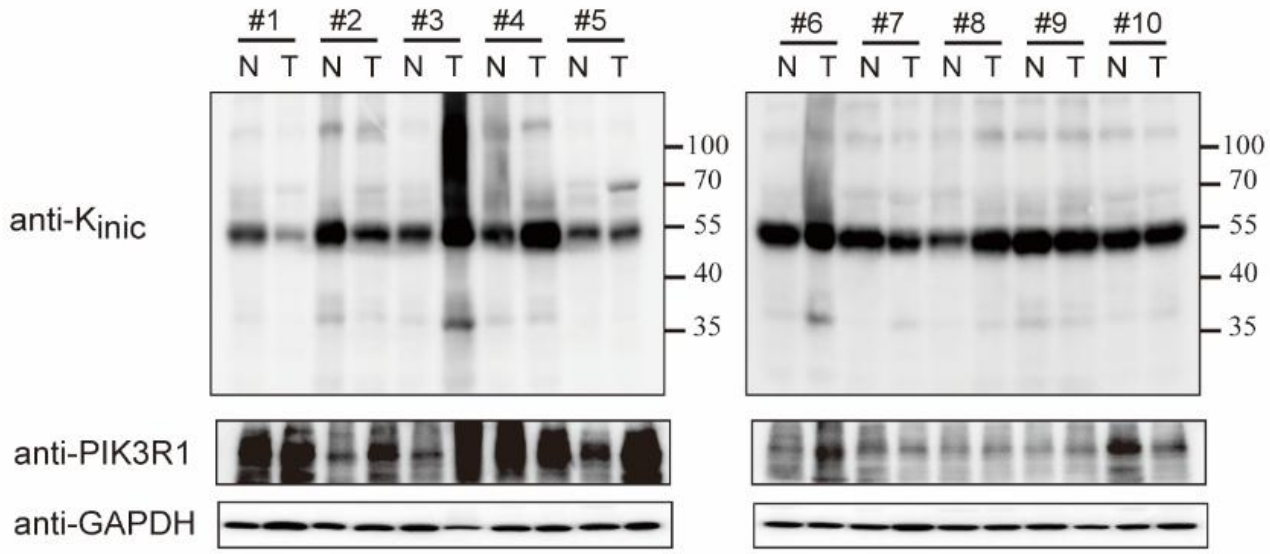
Conclusions: As a tumor suppressor, FOXA1 targets PIK3R1 directly to inhibit PI3K/Akt signaling pathway, thus exerting a negative regulatory effect on proliferation, migration, and invasion of HCC in male patients.

Keywords: FOXA1, Hepatocellular carcinoma, PIK3R1/PI3Kp85, PI3K/Akt

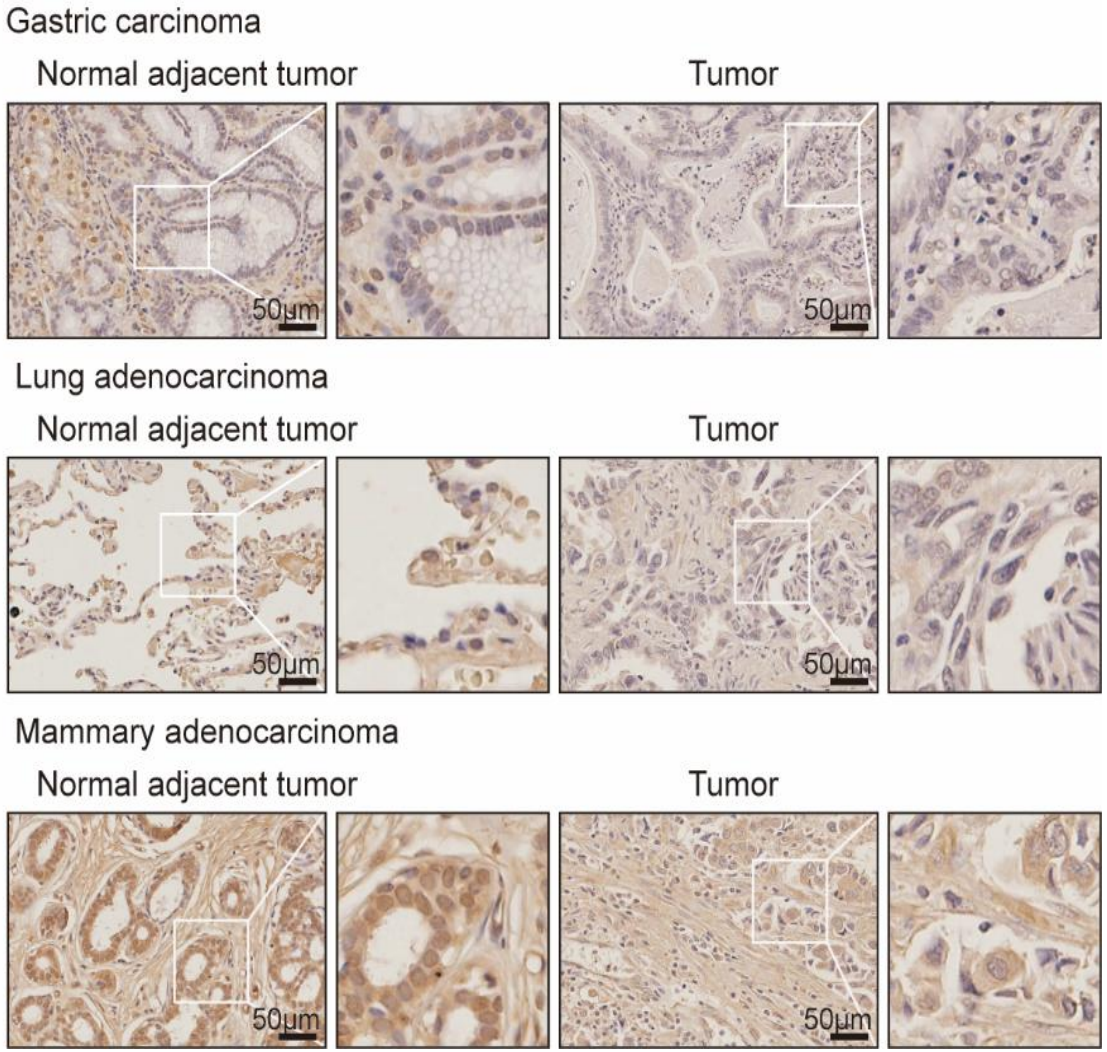
Histone isonicotinylation activates PI3K/Akt/mTOR

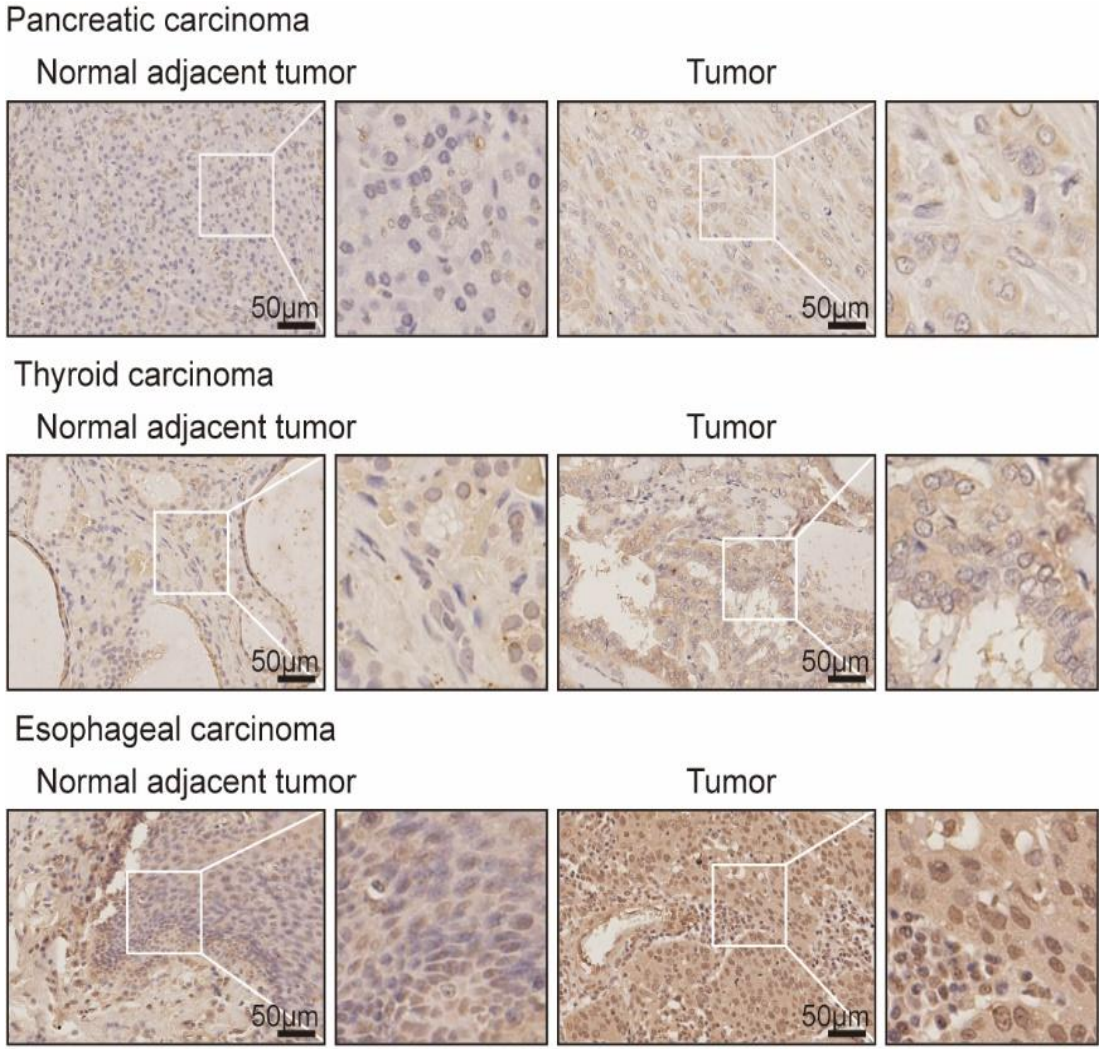




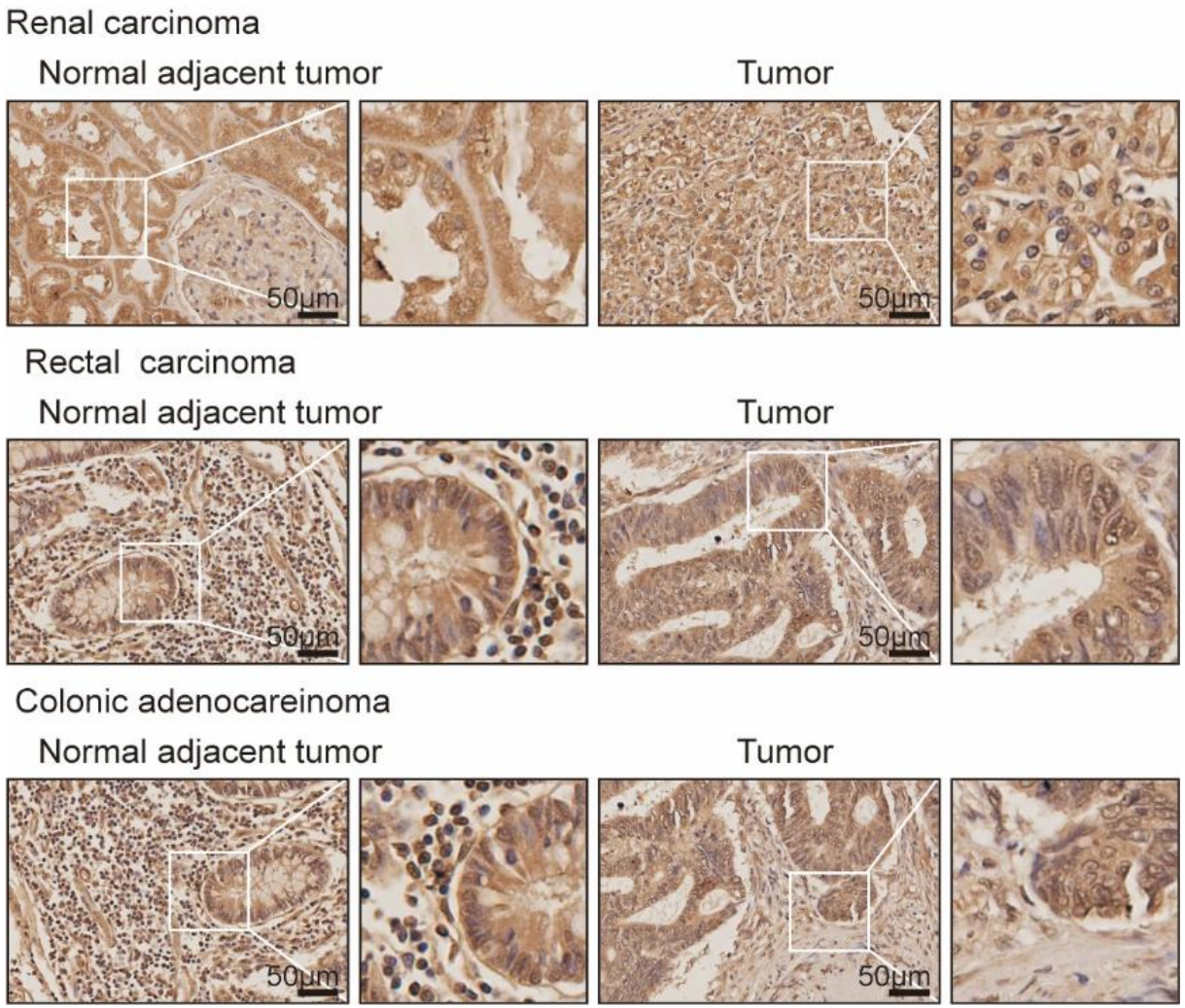


Histone isonicotinylation and tumor progression

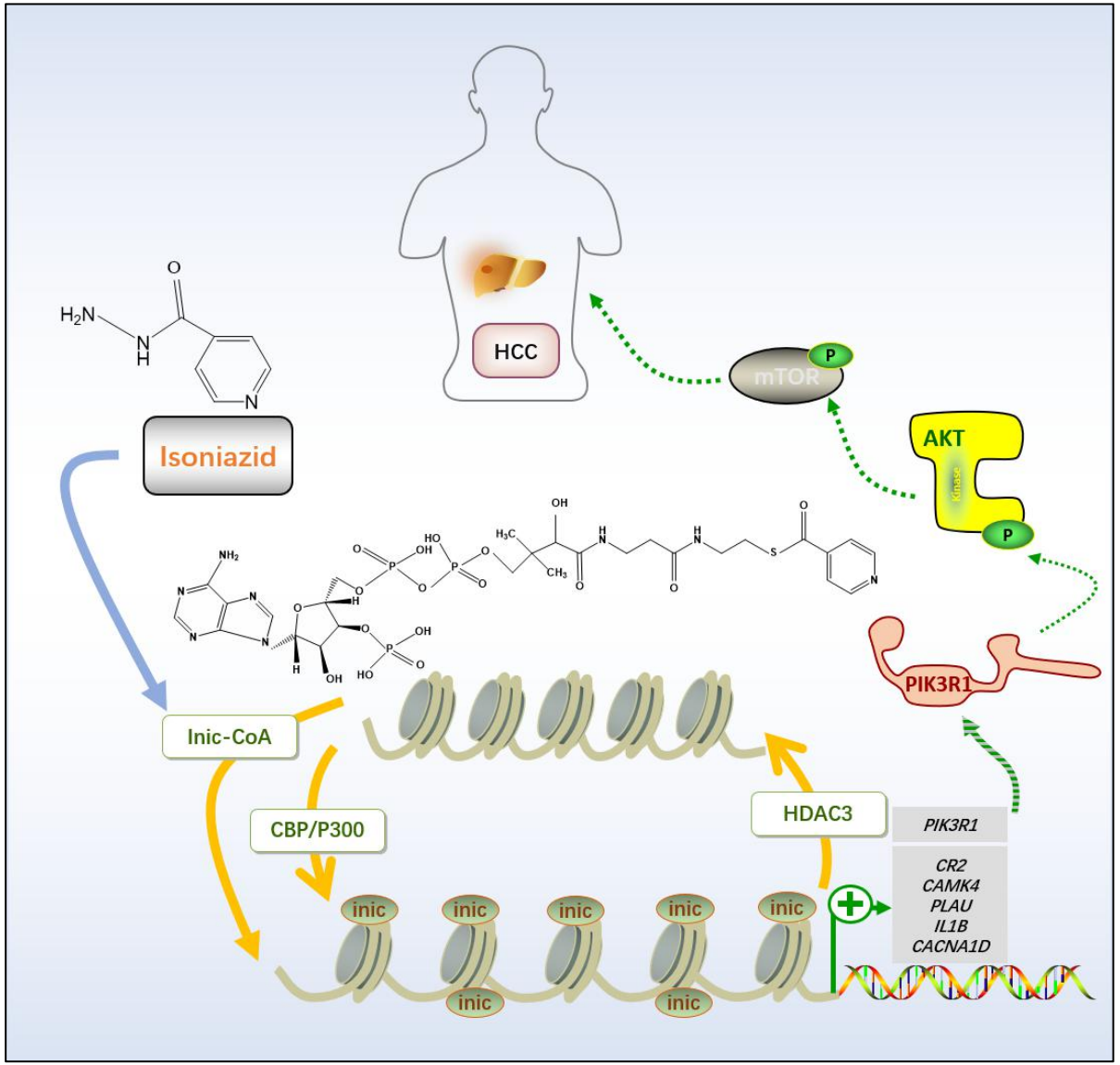




Histone isonicotinylation and tumor progression



Working model



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ARTICLE

https://doi.org/10.1038/s41467-021-25867-y OPEN

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Isonicotinylation is a histone mark induced by the anti-tuberculosis first-line drug isoniazid

Yuhan Jiang[1], Yixiao Li[1], Cheng Liu[1], Lei Zhang[1], Danyu Lv[1], Yejing Weng[2], Zhongyi Cheng[2], Xiangmei Chen[3], Jun Zhan[1] & Hongquan Zhang[1✉]

Isoniazid (INH) is a first-line anti-tuberculosis drug used for nearly 70 years. However, the mechanism underlying the side effects of INH has remained elusive. Here, we report that INH and its metabolites induce a post-translational modification (PTMs) of histones, lysine isonicotinylation (K_{inic}), also called 4-picolinylation, in cells and mice. INH promotes the biosynthesis of isonicotinyl-CoA (Inic-CoA), a co-factor of intracellular isonicotinylation. Mass spectrometry reveals 26 K_{inic} sites on histones in HepG2 cells. Acetyltransferases CREB-binding protein (CBP) and P300 catalyse histone K_{inic}, while histone deacetylase HDAC3 functions as a deisonicotinylase. Notably, MNase sensitivity assay and RNA-seq analysis show that histone K_{inic} relaxes chromatin structure and promotes gene transcription. INH-mediated histone K_{inic} upregulates *PIK3R1* gene expression and activates the PI3K/Akt/mTOR signalling pathway in liver cancer cells, linking INH to tumourigenicity in the liver. We demonstrate that K_{inic} is a histone acylation mark with a pyridine ring, which may have broad biological effects. Therefore, INH-induced isonicotinylation potentially accounts for the side effects in patients taking INH long-term for anti-tuberculosis therapy, and this modification may increase the risk of cancer in humans.

Jiang, et al. Nature Communications, 2021.9.20

结论

1. We identified histone isonicotinylation, a novel type of histone modification.
2. We identified 26 modification sites of histone isonicotinylation in HepG2 cell.
3. We showed that a histone acetyltransferase CBP/P300 has the function of histone isonicotinyltransferase, and a histone deacetylase HDAC3 has the function of histone deisonicotinylase.
4. Histone isonicotinylation loosens chromatin and may take effects in tumourigenesis and progression of liver cancer.

Laboratory of Cancer Metastasis