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Distinct classes of selenium-containing proteins in carcinogenesis and prevention

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Introduction

There are three classes of selenium-containing proteins:

1. **A protein that contains selenomethionine in which selenium incorporates non-specifically into the sulfur-containing amino acid (due to its structural similarity to sulfur);**

2. **Selenoproteins: these proteins contain the amino acid selenocysteine (Sec), e.g. glutathione peroxidases (GPx-1, GPx-2, GPx-3 and GPx-4), selenoprotein P, selenoprotein W, etc;**

3. **Selenium-binding protein: human, hSBP1, SELEBP; mouse, SBP1, SBP2.**

Identification of selenium-binding protein:

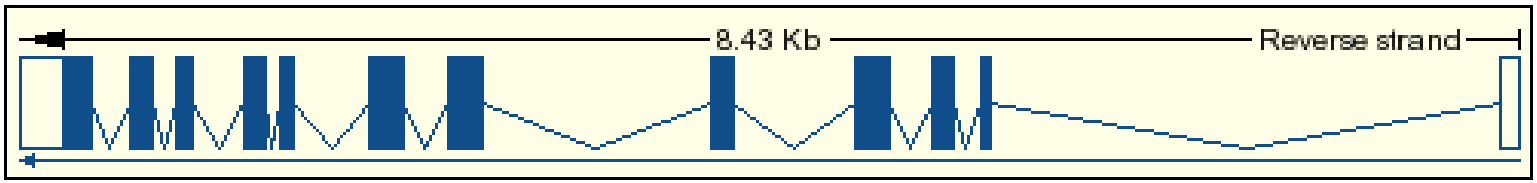
SBP1 was discovered in rat liver and intestinal tract (Banerjee et al, BBRC, 1982; Sani, et al. Carcinogenesis. 1988; Morrison, et al, *In vivo*. 1989)

The selenium-binding proteins were different from selenoproteins (glutathione peroxidase, etc)

SBP1 was found to have anti-cancer function via binding selenium in mice (Bansal, et al, Carcinogenesis, 1990)

Human SBP1 was cloned and characterized in 1997 (J. Cell. Biolochem, 1997, 64: 217)

Genomic location: Chromosome 1 at location 149,603,402-149,611,833
Transcription: Exons: 12; Transcript length: 1,752 bps;
Translation length: 472 residues

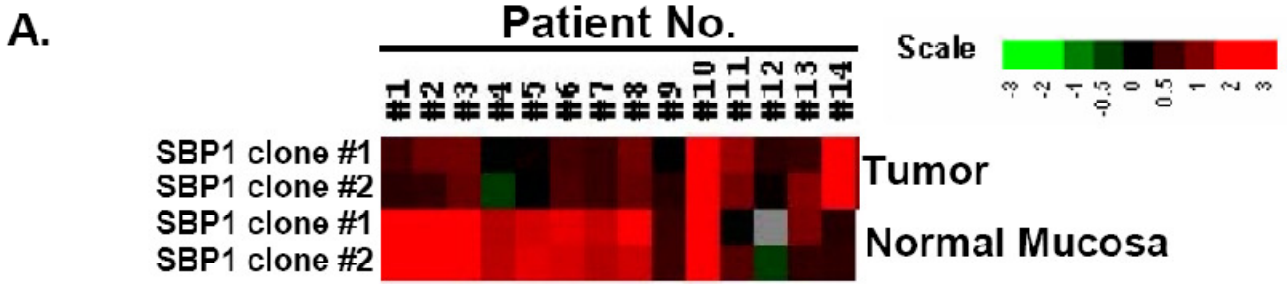


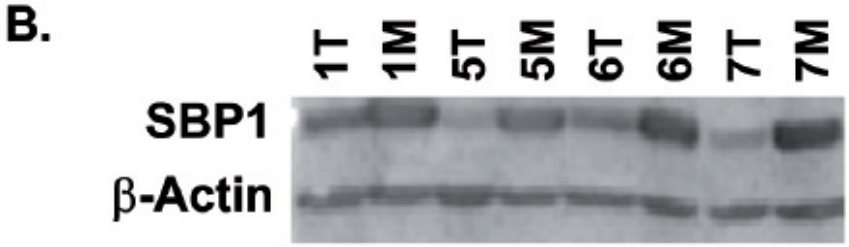
SBP1 and Cancers:

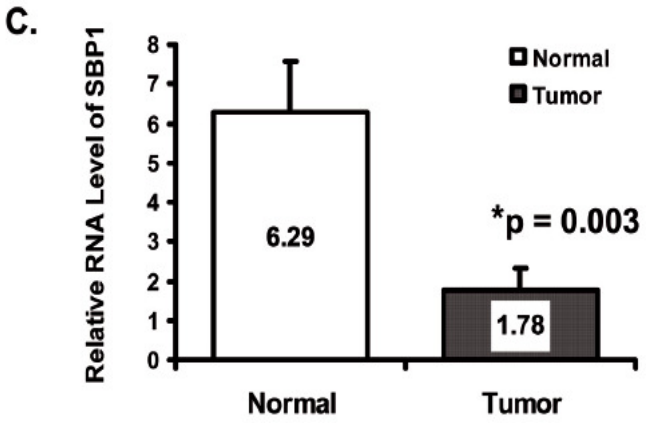
SBP1 expression is reduced in human cancer tissues and the reduction of SBP1 in cancer is associated with poor survival:

1. **Prostate cancer** (Yang, *Cancer Res*, 1998, 58: 3150-3)
2. **Lung cancer** (Chen et al, *J Pathol*, 2004, 202: 321-9)
3. **Pleural Mesothelioma** (Pass et al,*Clin. Can.Res.*, 2004, 10:849-859)
4. **Ovarian cancer** (Huang et al, *Int J Cancer*, 2006, 118: 2433-40; Zhang et al, *Hum Pathol*, 2010, 41: 255-61)
5. **Colorectal cancer** (Li et al, *Proc.AACR*, 2005; Kim et al, *Proteomics*, 2006, 6: 3466-76; Li et al, *Mol Nutr Food Res*, 2008);
6. **Thyroid cancer** (Brown et a, Mol. *Carcinogenesis*, 2006, 45: 613-626)
7. **Esophageal cancer** (*Silvers et al, Clin Can. Res, 2010, 16: 2009-21*)
8. **Gastric cancer** (Zhang et al, *Med. Oncol*, 2010, Jun;28(2):481-7)

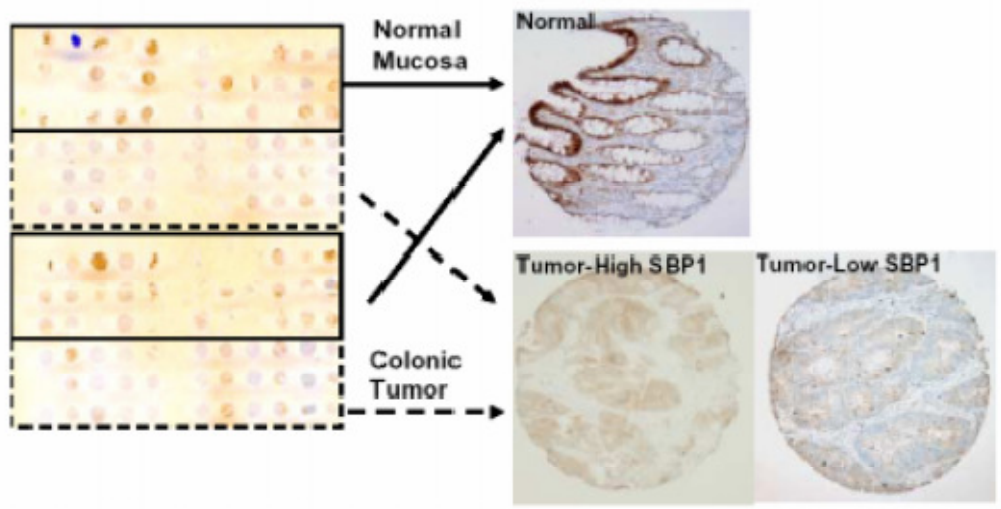
SBP1 expression was reduced in colonic carcinomas v.s. normal mucosa







Decreased expression of SBP1 in colorectal cancer was associated with poor survival



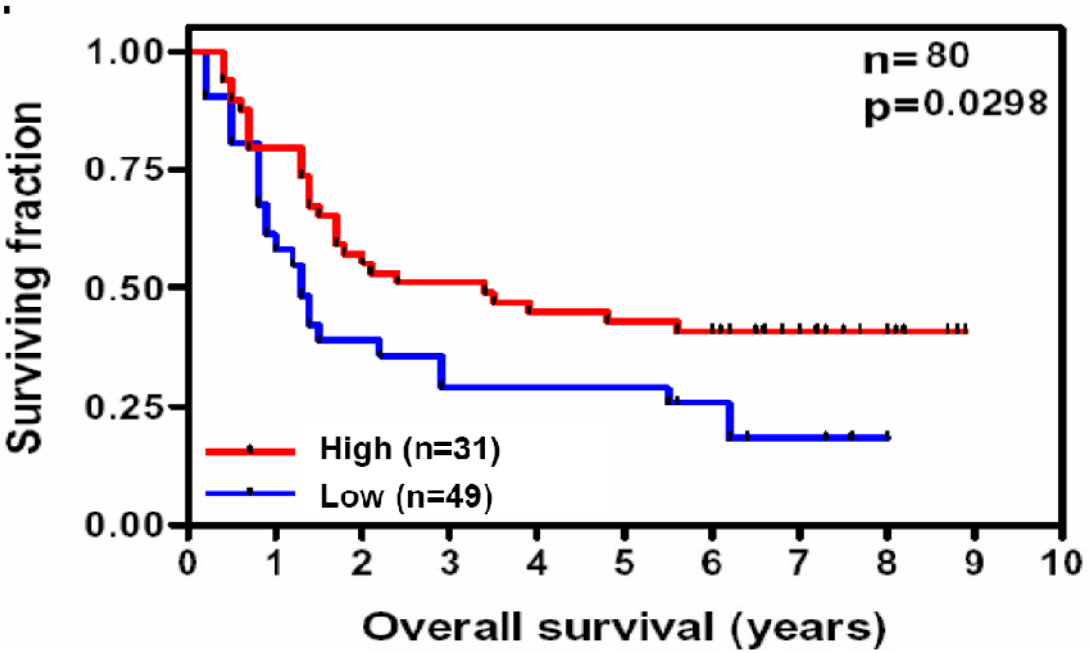


Table 1. Clinicopathological features of 80 eligible colorectal cancer patients in the tissue microarray study.

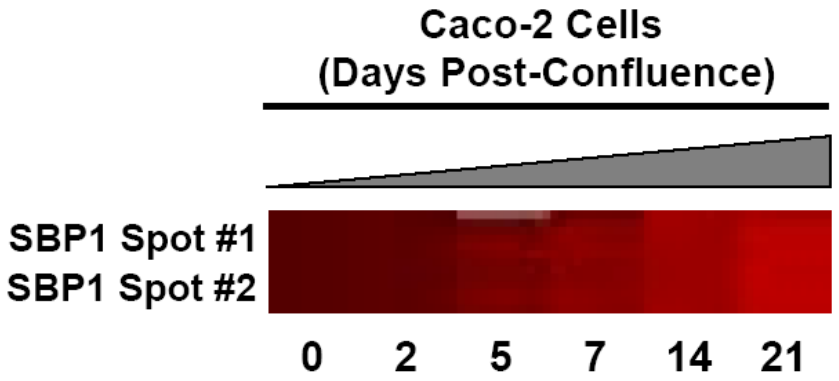
Categories	Tumors with low SBP1 level (<22.5)	Tumors with high SBP1 level (≥ 22.5)	Significance
No. of Patients (n=80)	49	31	
Median age, years	72.0	71.0	p=0.65[a]
Range	40-88	45-86	
Gender			
Female (%)	25 (51%)	16 (51.6%)	
Duke Stage			
A	0	1	
B	3	1	
C	44	29	
D	2	0	
Median Grade (1-3)	2.0	2.0	p=0.34[a]
Tumor Location			
Colon	24 (49%)	18 (58%)	
Rectum	24 (49%)	13 (42%)	
Unknown	1 (2%)	0 (0%)	
Median Follow-up, years	9.2	9.9	p=0.12[a]
Tumor SBP1 expression	6.67	46.67	p=6.84E-20[a] *
Tumor : Normal SBP1 Level	0.19	1.00	p=5.51E-09[a] *
Disease-Free Survival, years	0.8	2.5	p=0.04[b] *
Overall Survival, years	1.4	3.5	p=0.03[b] *

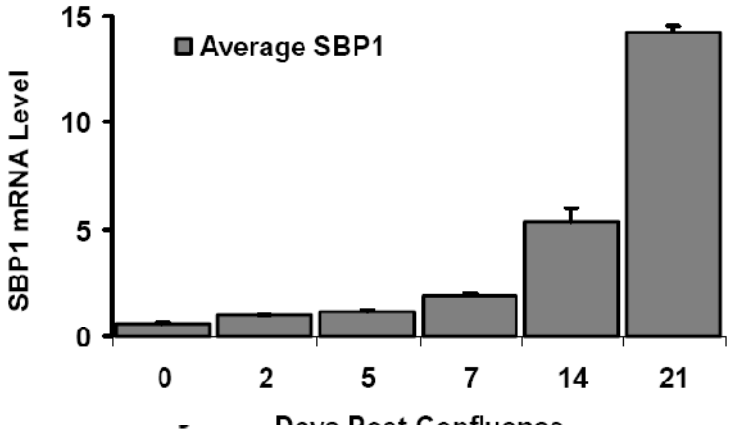
[a] Unpaired Student's t-test

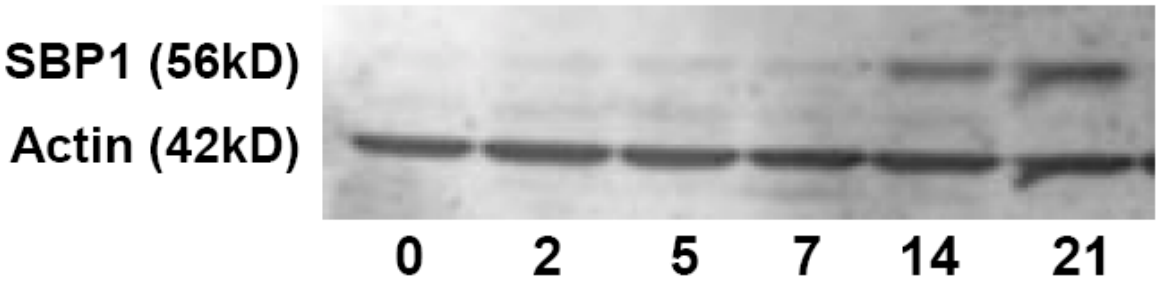
[b] Cox regression analysis

* indicates statistically significant differences that are defined as a two-sided p value <0.05.

SBP1 expression was upregulated during cell differentiation

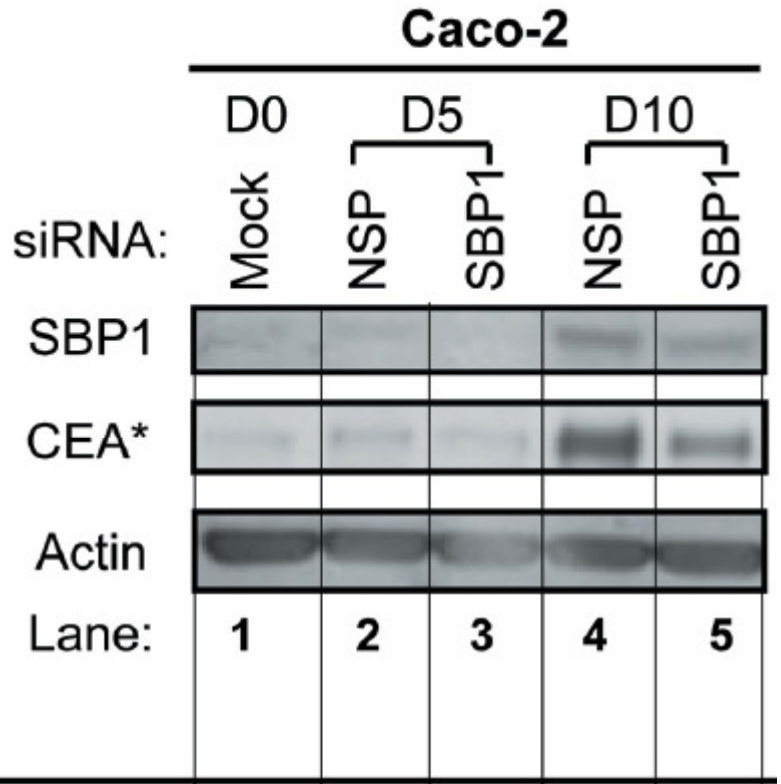






Knockdown SBP1 by siRNA delayed cell differentiation in colon cancer cells

A.



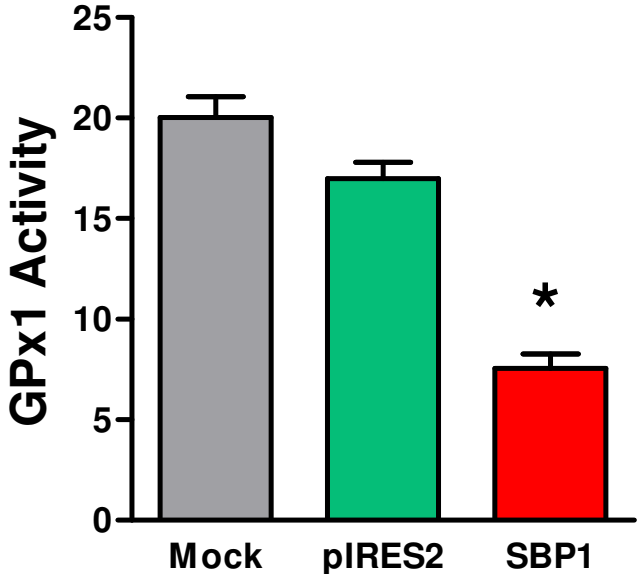
B.

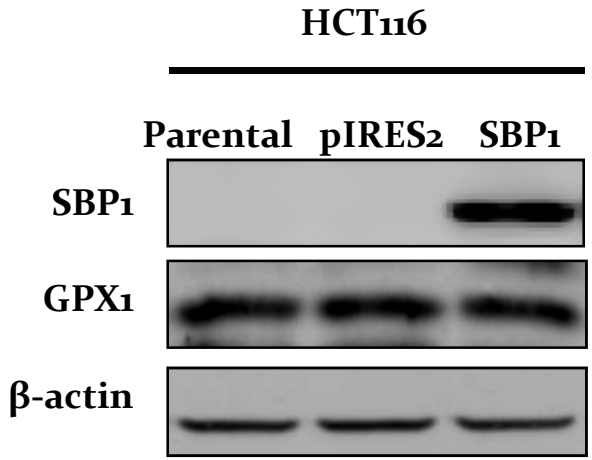
SBP1/Actin:	**1.0**	**2.8**	**1.1 ↓62%**	**22.6**	**12.0 ↓47%**
CEA*/ Actin:	**1.0**	**3.1**	**1.7 ↓44%**	**20.5**	**10.5 ↓49%**

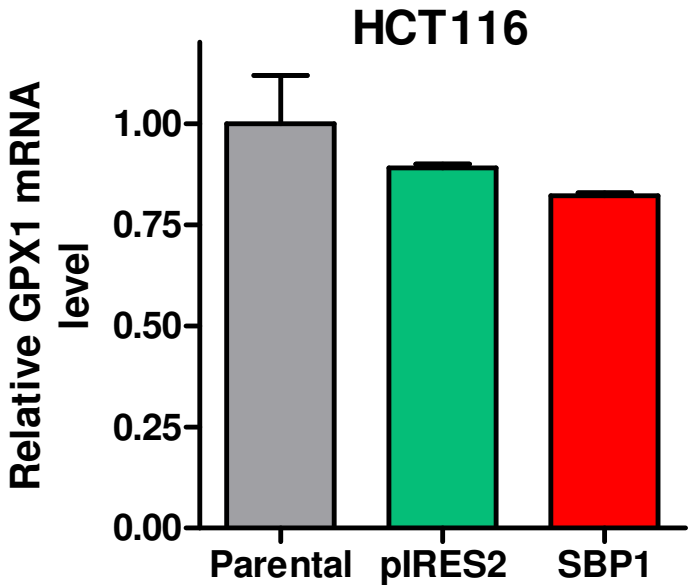
Li et al, *Mol Nutr Food Res*, 2008

Functional interaction between SBP1 and GPX1

SBP1 inhibited GPX1 activity , but did not affect GPX1 protein and mRNA levels

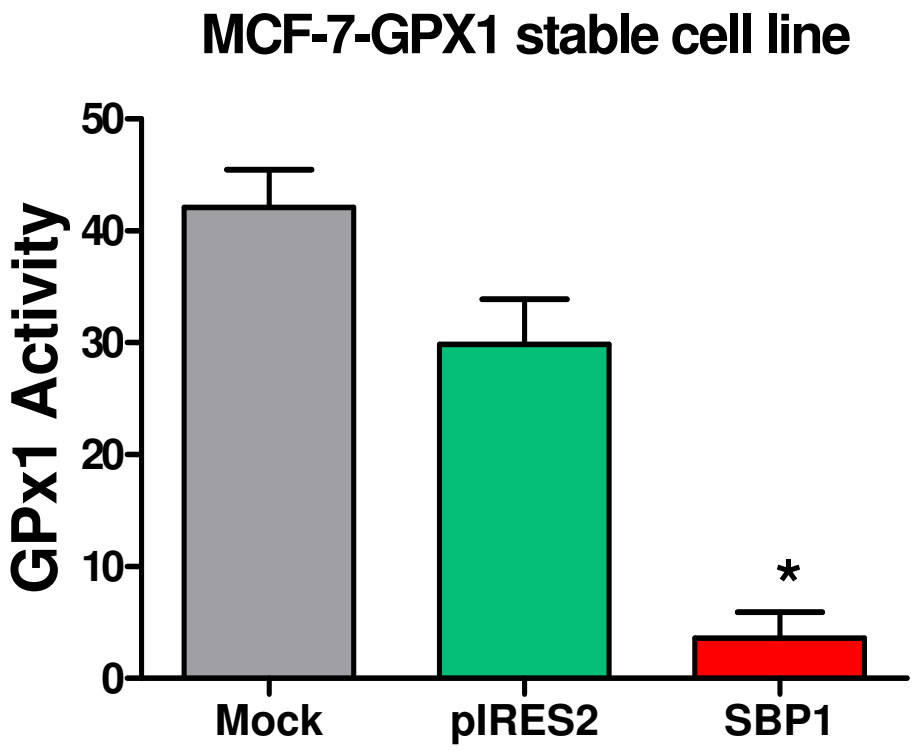




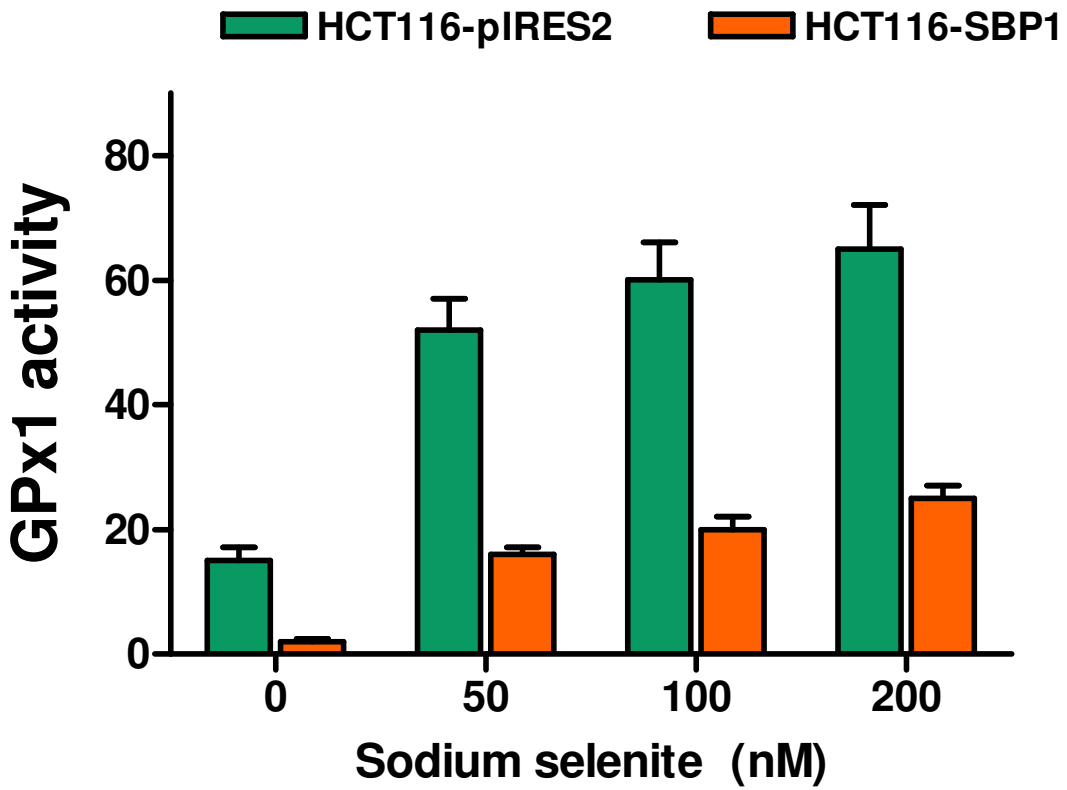


Fang et al, Carcinogenesis, 2010

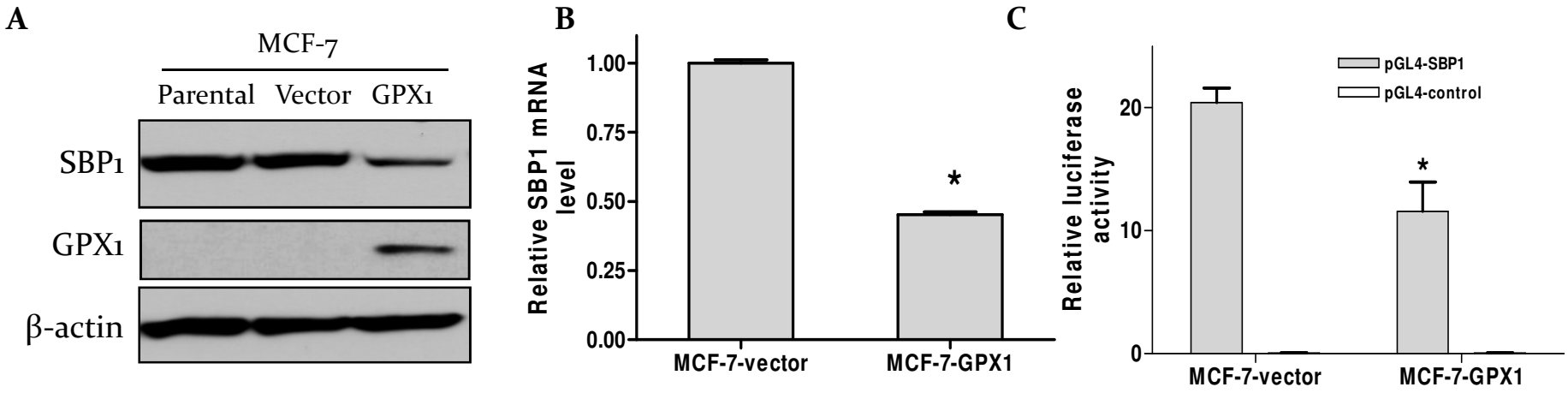
SBP1 inhibited GPX1 activity in breast cancer cells

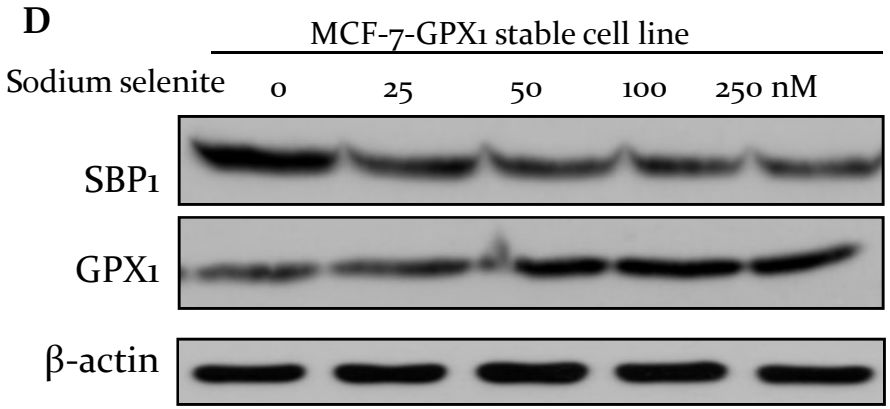


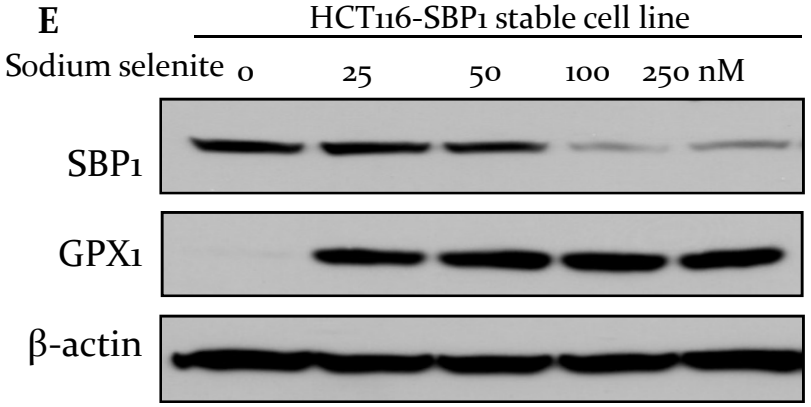
SBP1 overexpression inhibited selenium-induced GPX1 activity in colon cancer cells



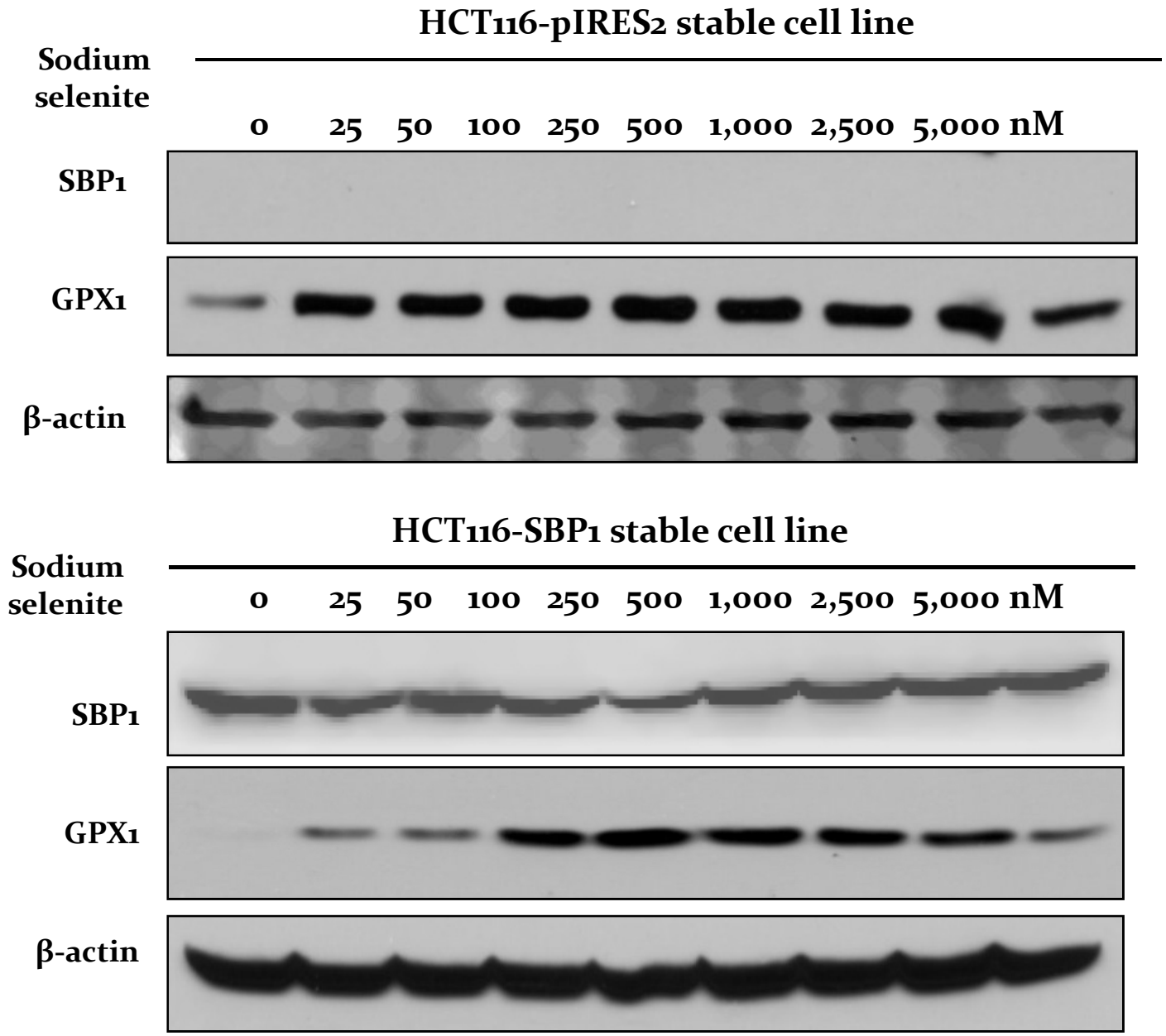
GPX1 inhibited SBP1 expression in translational and transcriptional levels.



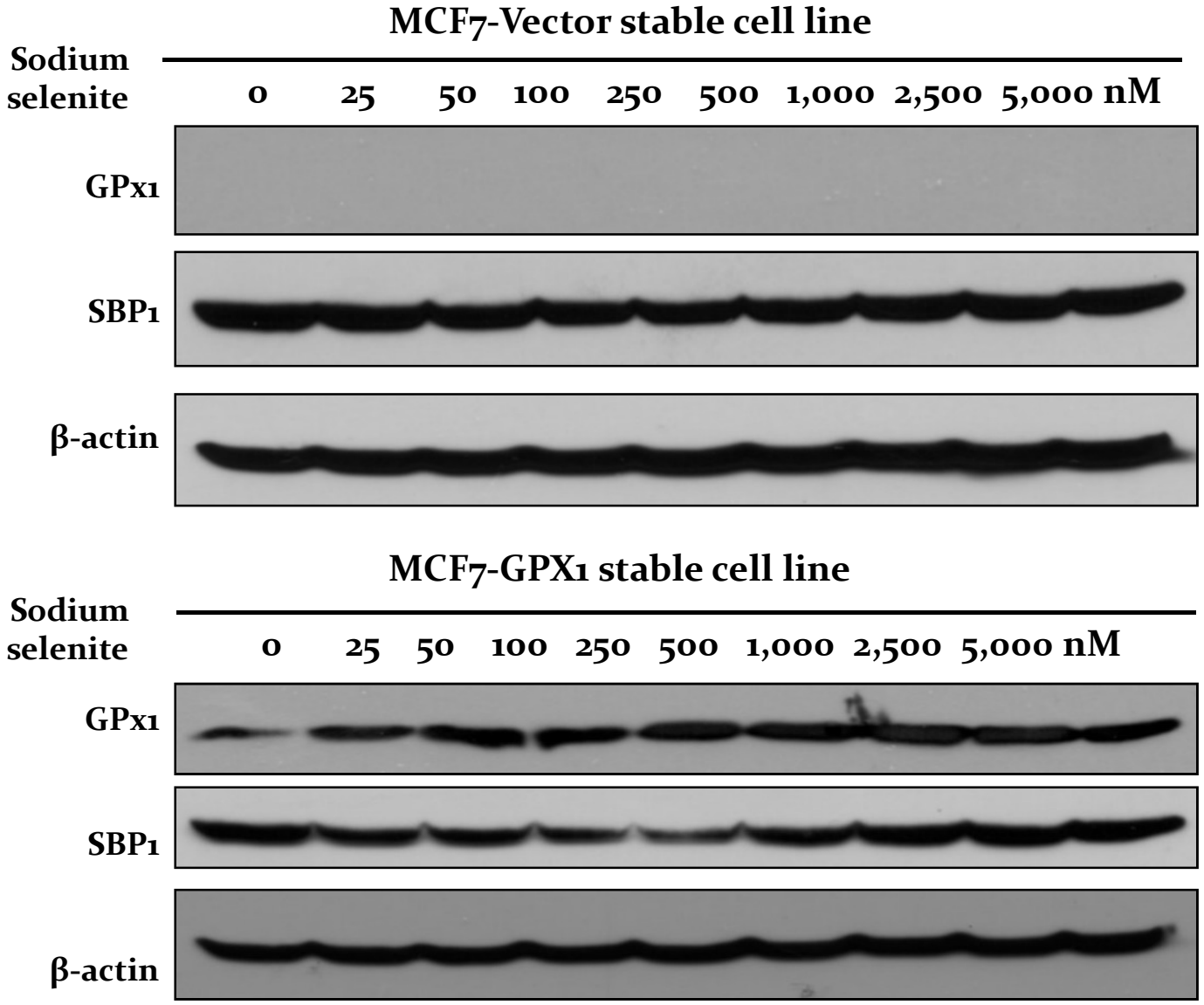




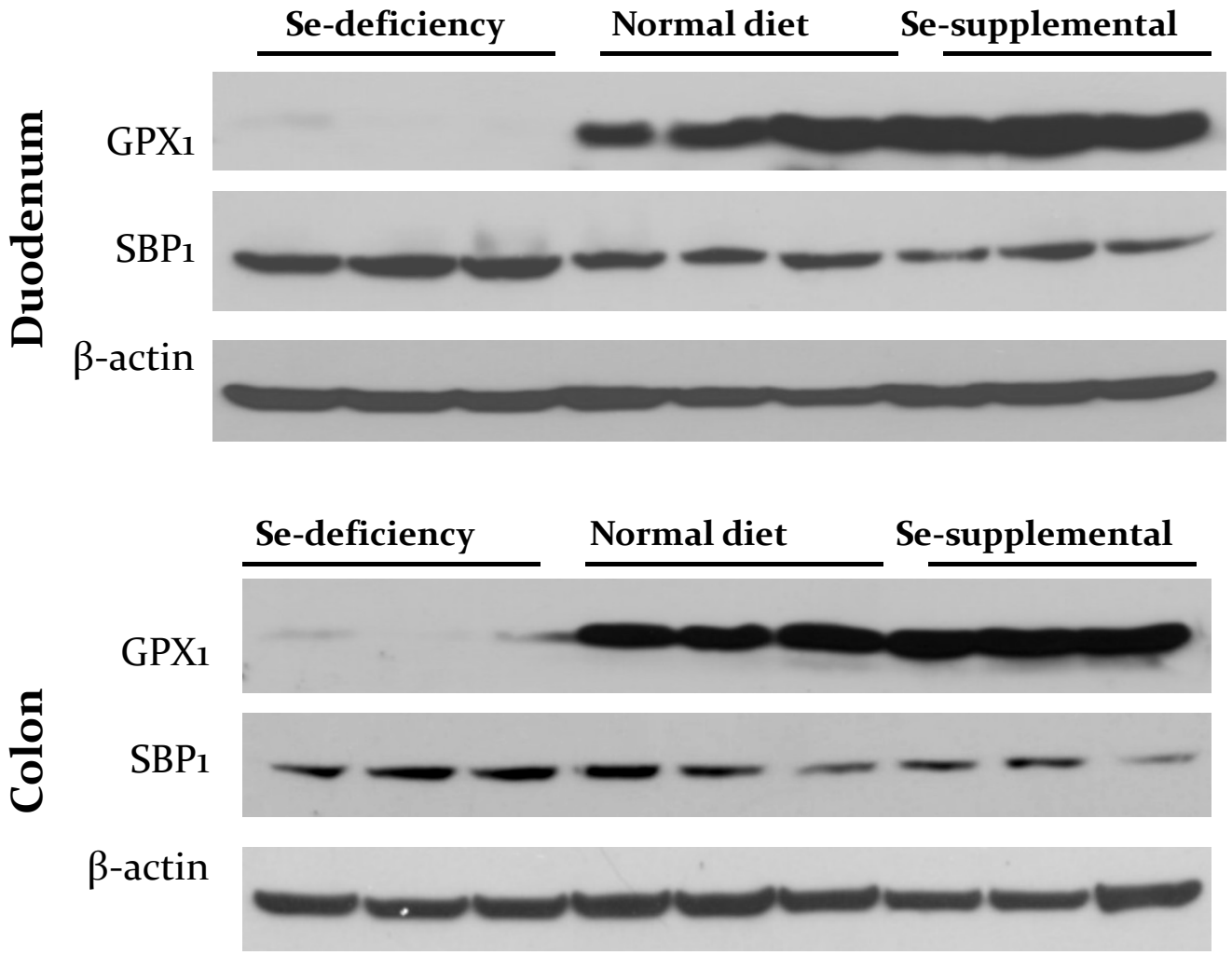
SBP1 affects selenium-mediated alterations of GPX1



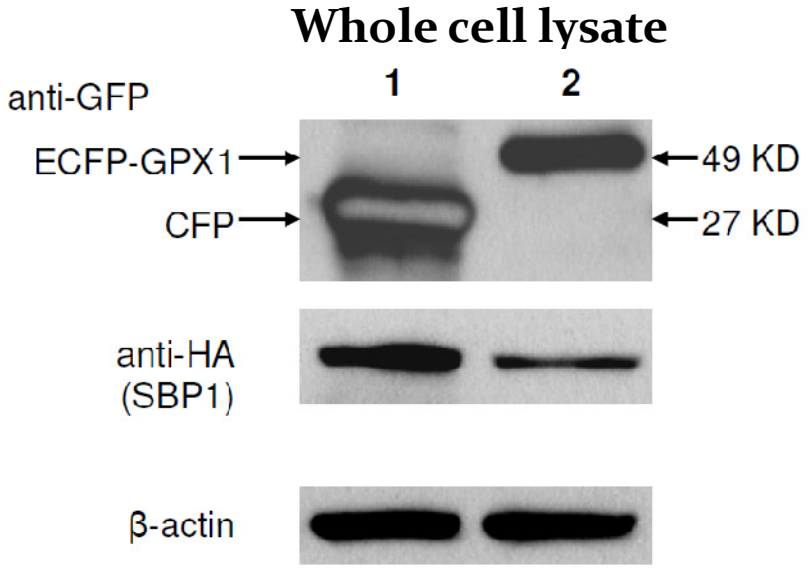
Selenium-mediated alterations of GPX1 affects SBP1



GPX1 and SBP1 expression in mouse intestinal epithelial cells (3 mice/group)

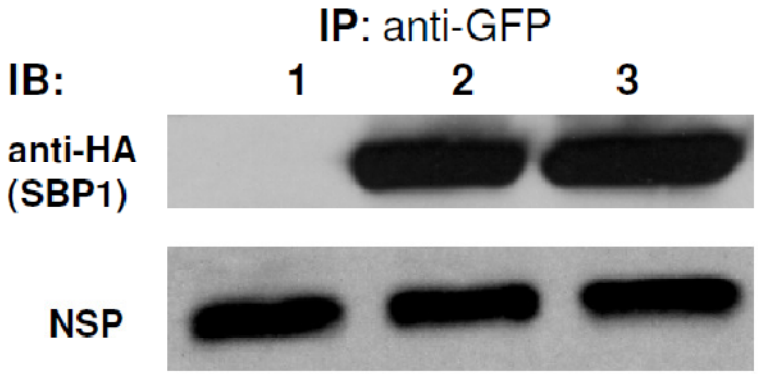


Physical interaction between SBP1 and GPX1



1.HA-SBP1+pECFP

2.HA-SBP1+pECFP-Sec-GPX1

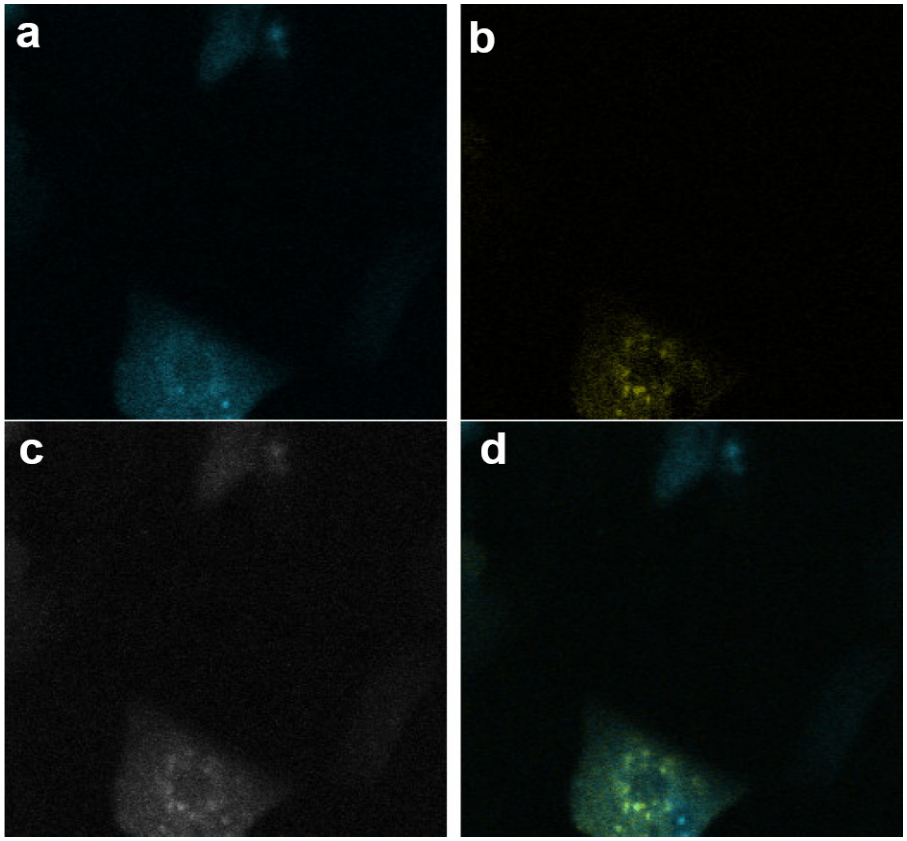


1.HA-SBP1+pECFP

2.HA-SBP1+pECFP-Sec-GPX1

3.HA-SBP1+pECFP-Cys-GPX1

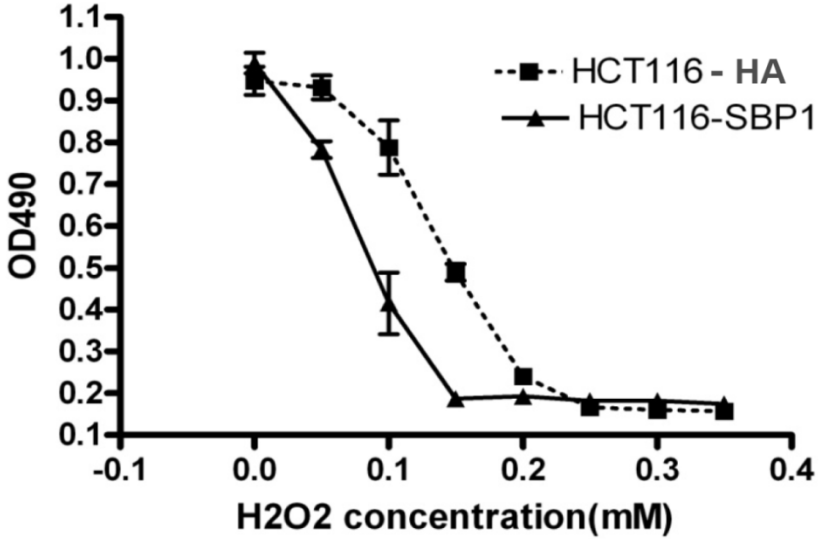
Co-localization of SBP1 and GPX1 in cytoplasm detected by FRET (confocal microscope)

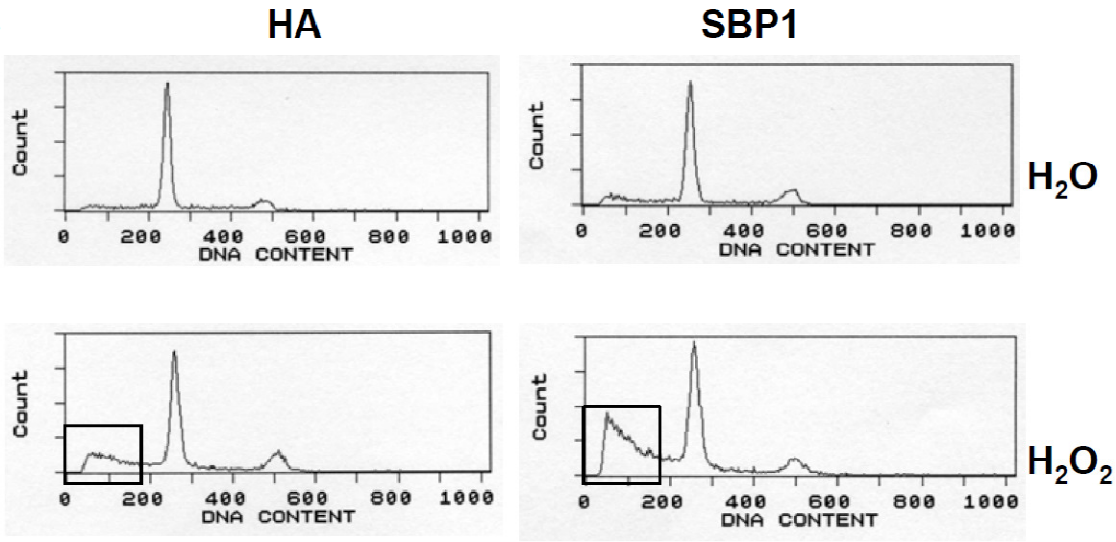


a. Before photobleaching
b. After photobleaching detect YFP-SBP1
c. After photobleaching detect CFP-GPx1
d. After photobleaching detect merge image

Anti-oxidant and Tumor Suppression

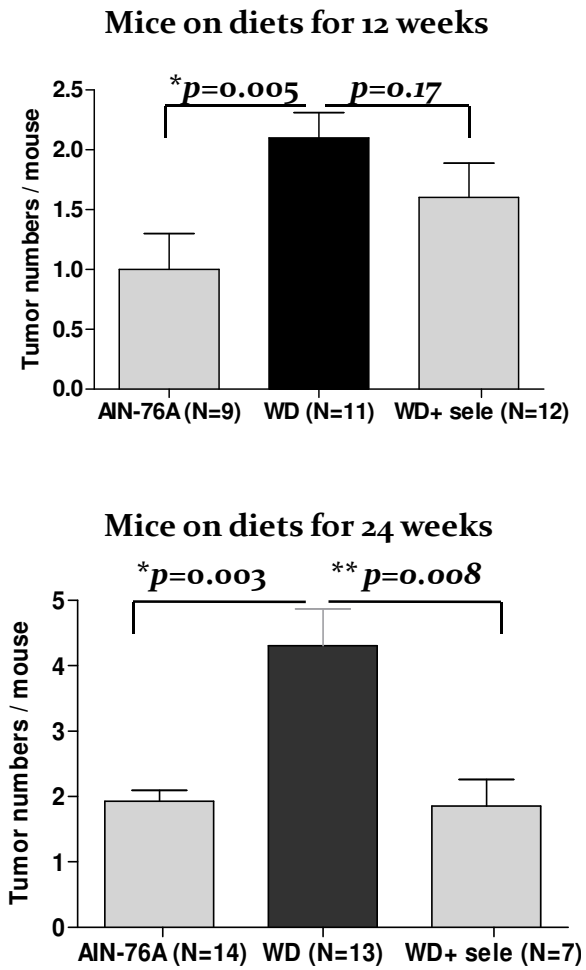
SBP1 accelerates H2O2-induced cell death





Selenium-supplementation prevented intestinal tumor formation in Muc2/P21 mice through JNK1 phosphorylation and inhibition of beta-catenin and COX2

A



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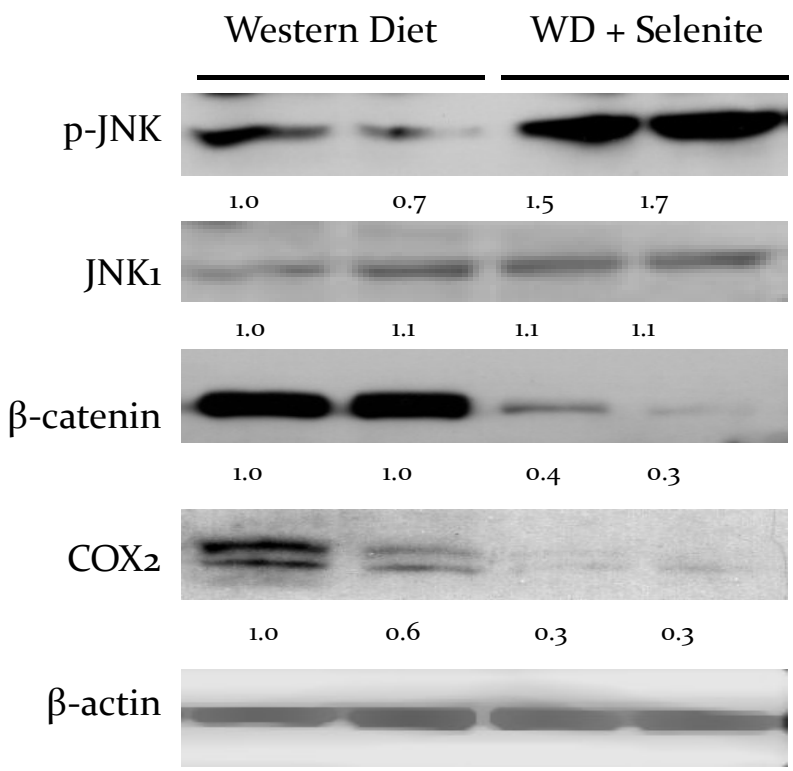
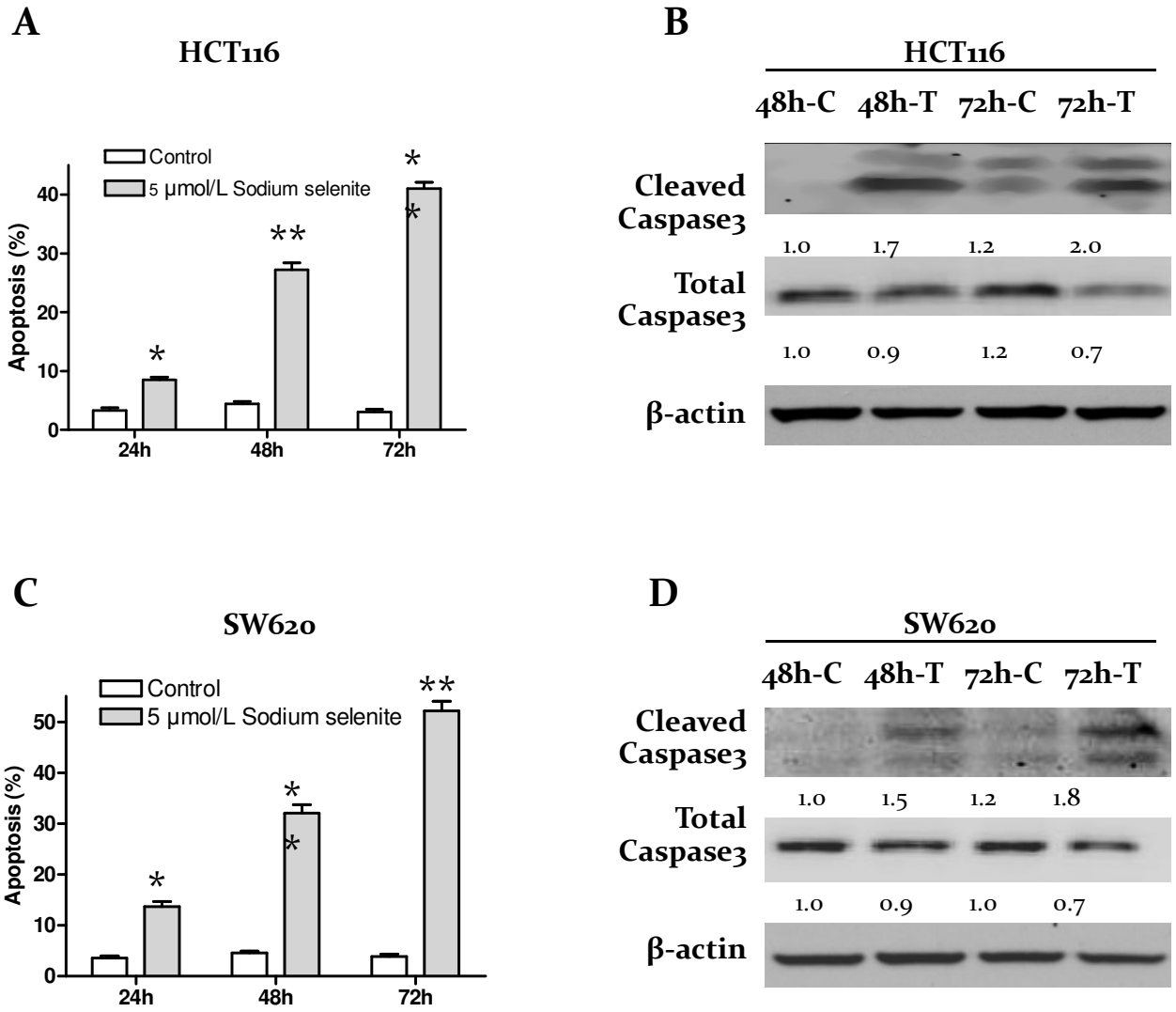
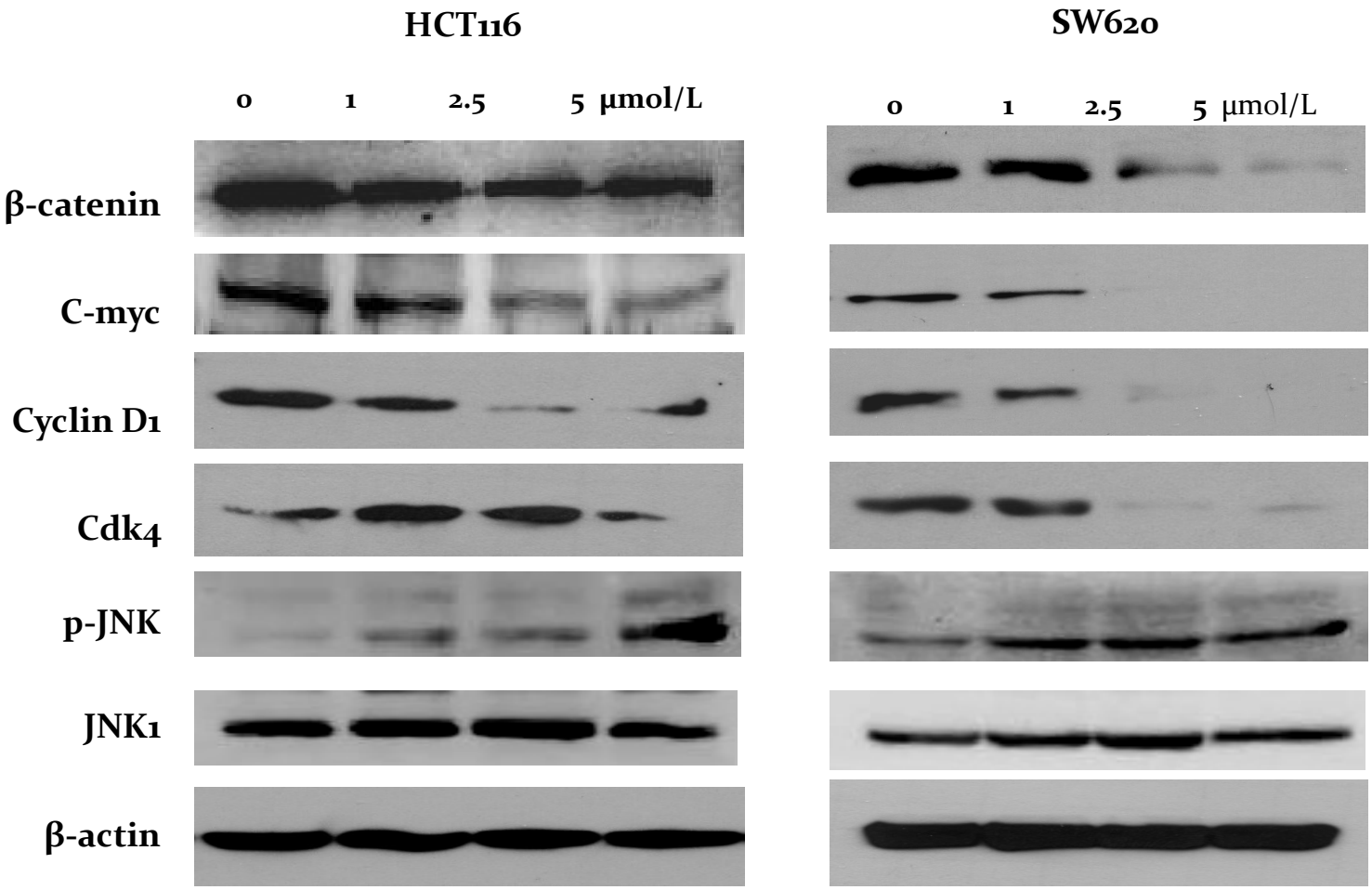


Sodium selenite promoted apoptosis in colon cancer cells

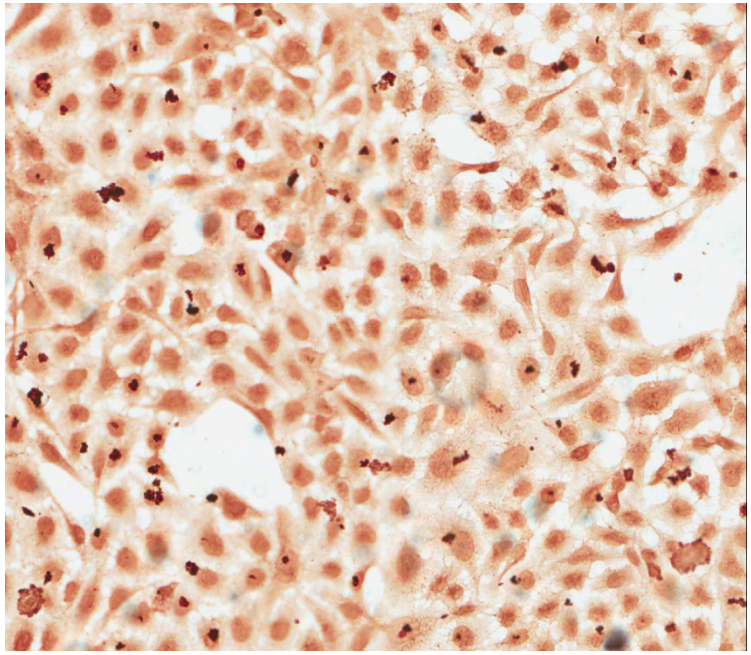


Sodium selenite suppressed beta-catenin signaling and increased JNK1 phosphorylation in vitro

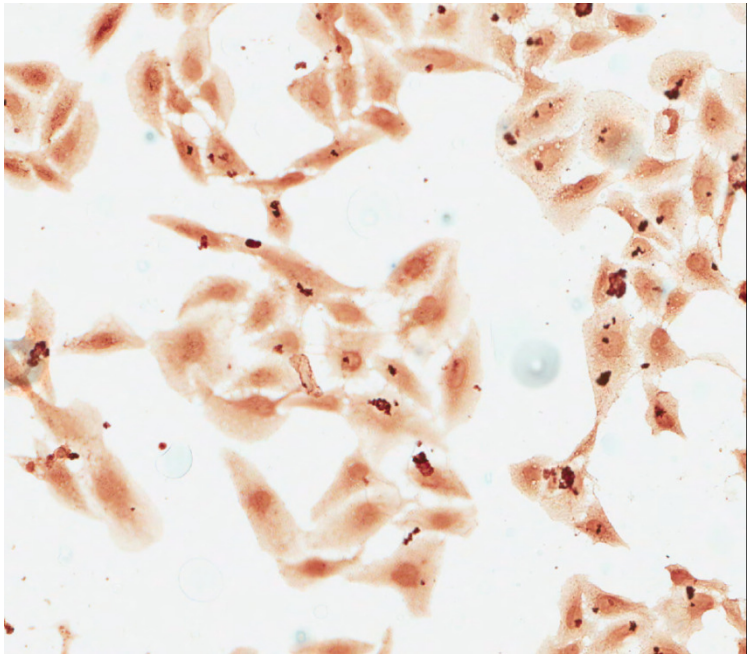


Sodium selenite degraded beta-catenin in osteosarcarmo cells U2OS

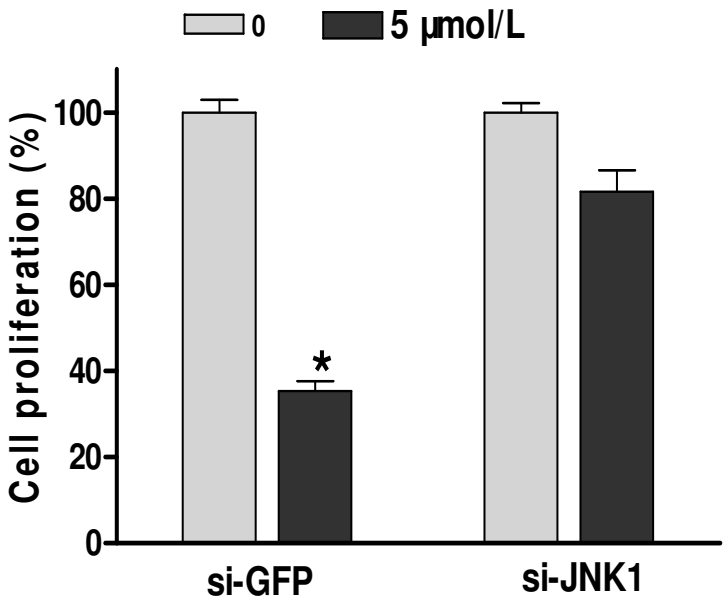
Control

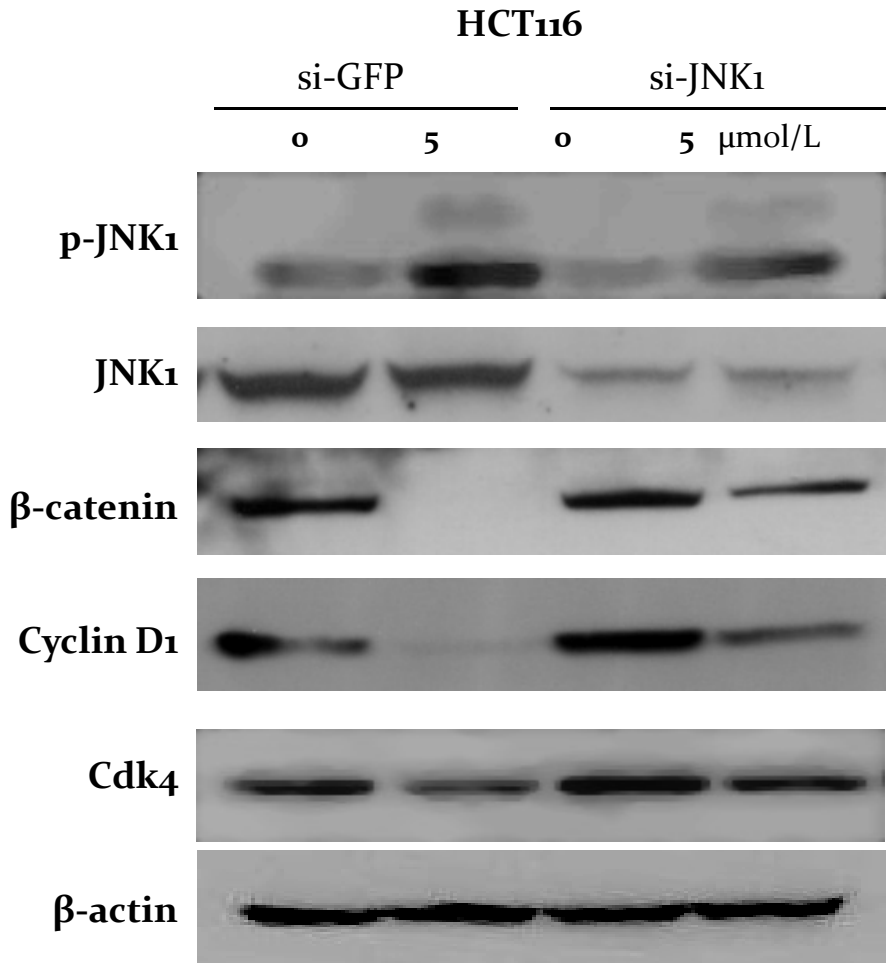


5 μM sodium selenite



Reduced JNK1 expression attenuated selenium-mediated inhibition of cell proliferation





Summary

- SBP1 expression is reduced in colon cancer, reduced expression of SBP1 in cancer predicts poor outcome;
- There is a direct interaction and negative regulation between SBP1 and GPX1;
- Decreased SBP1 transcription and translation by TGF-beta was linked to reduced p21 expression and JNK1 phosphorylation, to increased GPx1 and beta-catenin in vitro;
- Selenium-mediated cancer prevention is associated with JNK1 phosphorylation and inhibition of beta-catenin *in vitro* and in mouse model of colon cancer.

Li , et al. Mol Nutr Food Res, 2008;
Fang, et al. Int. J. Cancer, 2010;
Huang, et al. Int J Mol Med. 2012
Ansong et al, Mol Nutr Food Res, 2014

Pohl, et al. PloS ONE, 2009
Fang et al, Carcinogenesis, 2010
Yang et al, Biomarker Res. 2013

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