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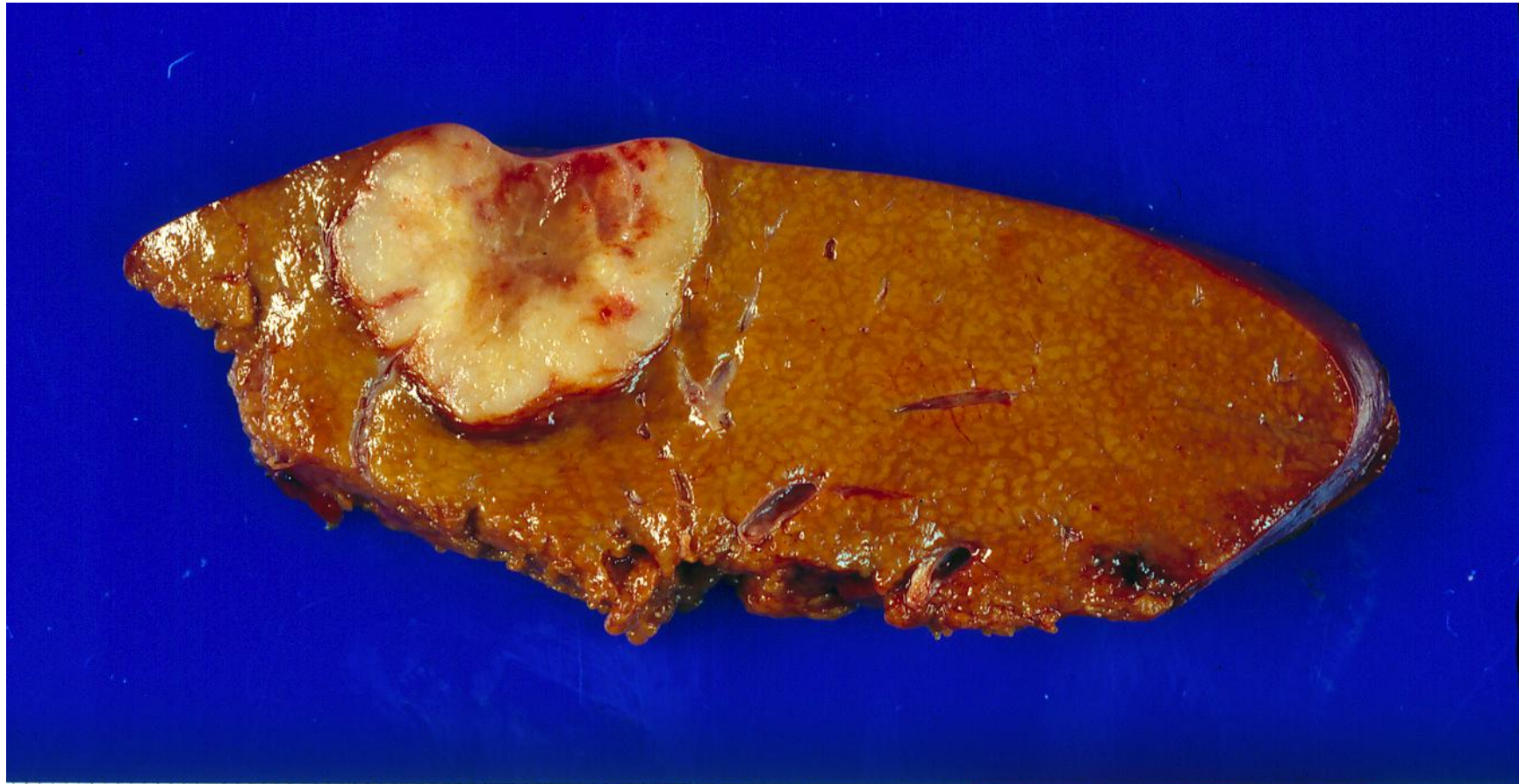
# **Biphasic Pattern and Terminal Switch of Lipid Metabolomics in HBV Tumorigenesis: *Implication for cancer chemoprevention***

*Ih-Jen Su, MD, PhD*

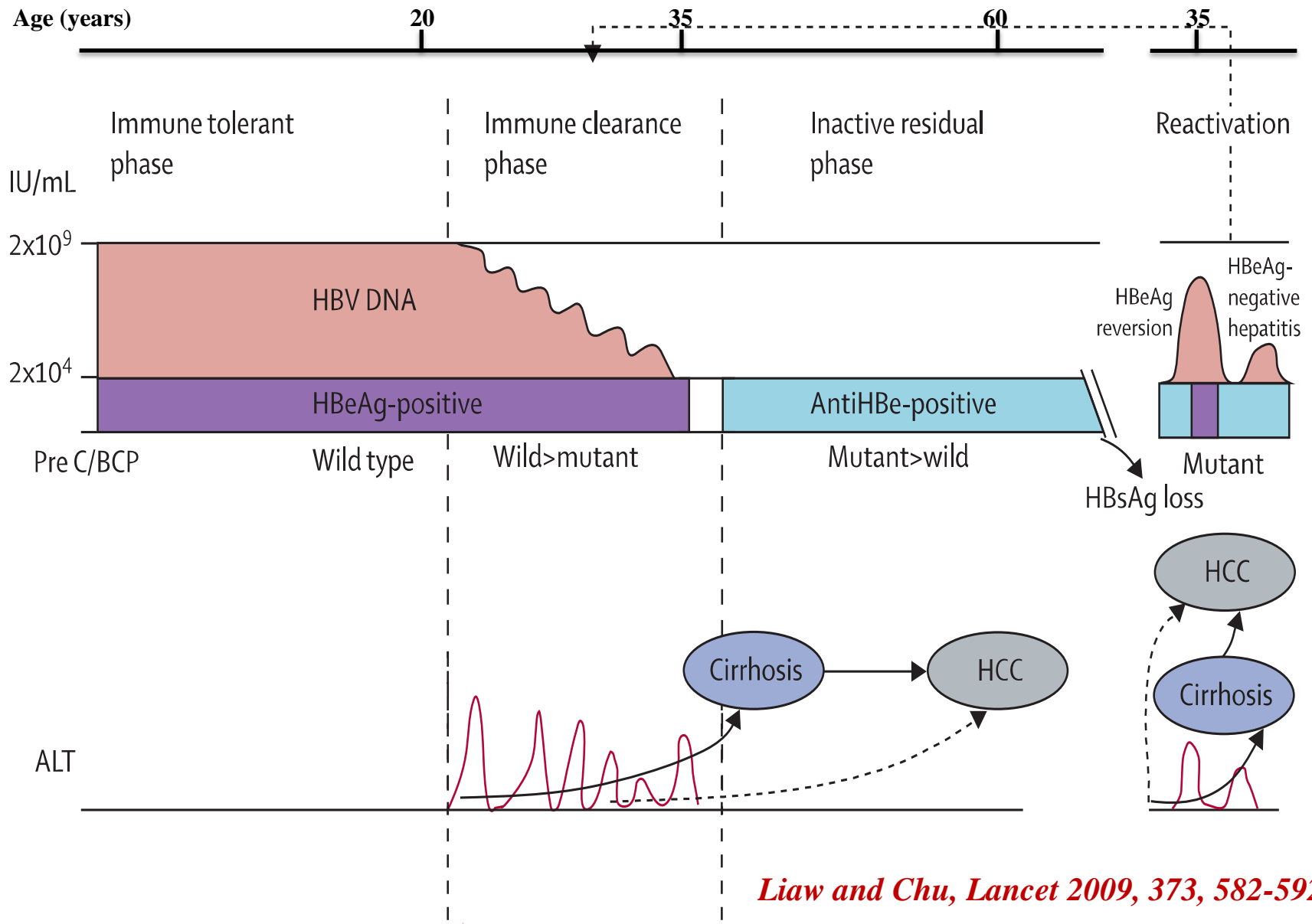
Department of Pathology, National Cheng Kung  
University Medical School and Hospital  
National of Infectious Diseases Institutes and  
Vaccinology, National Health Research Institutes;

**Metabolomics and System Biology Symposium, 27 April,  
Philadelphia, USA**

**HBV-associated Hepatocellular Carcinoma** Remains the Major Cancer Mortality in Taiwan and Chemopreventive Agents Targeting at the Driving Signal Is urgently Needed for High Risk Patients of Chronic HBV Infection



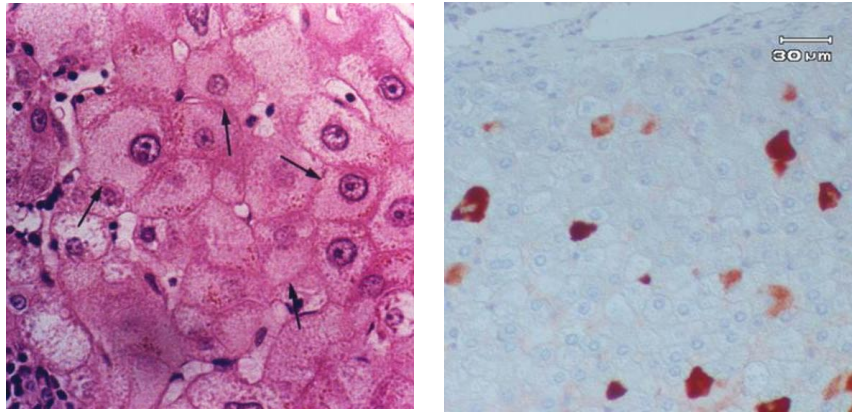
# Natural Course of Chronic HBV Infection





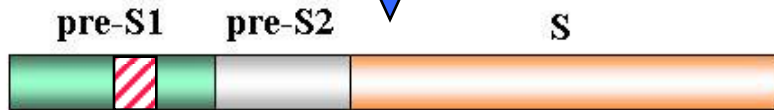
In **2000**, we identified HBV Pre-S2 deletion mutant large surface antigen (**Pre-S2 mutant**) which is accumulated in endoplasmic reticulum (**ER**) of Type 2 ground glass hepatocytes (**GGH**) as a **new viral oncoprotein** in HBV Tumorigenesis, besides **HBx**

### Type I GGHs



(H&E staining)

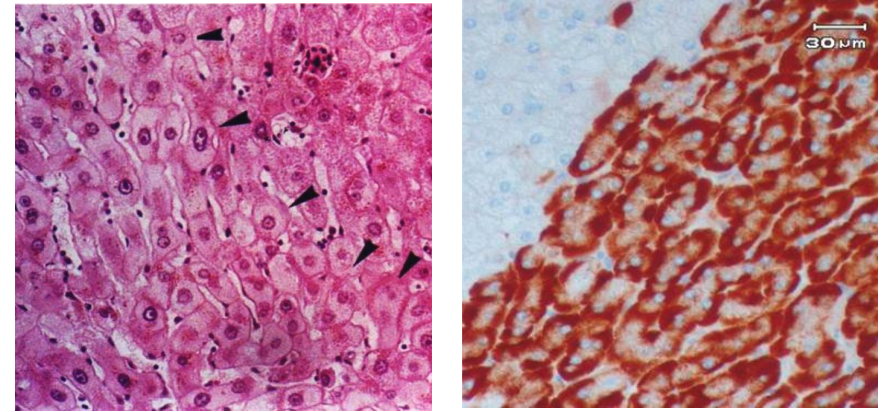
(IHC staining)



**Pre-S1 deletion mutant**

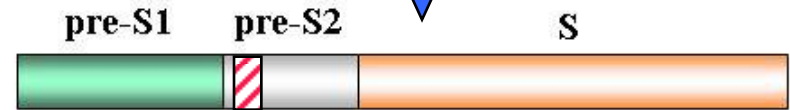
deletion region: 

### Type II GGHs



(H&E staining)

(IHC staining)



ATG → ATA

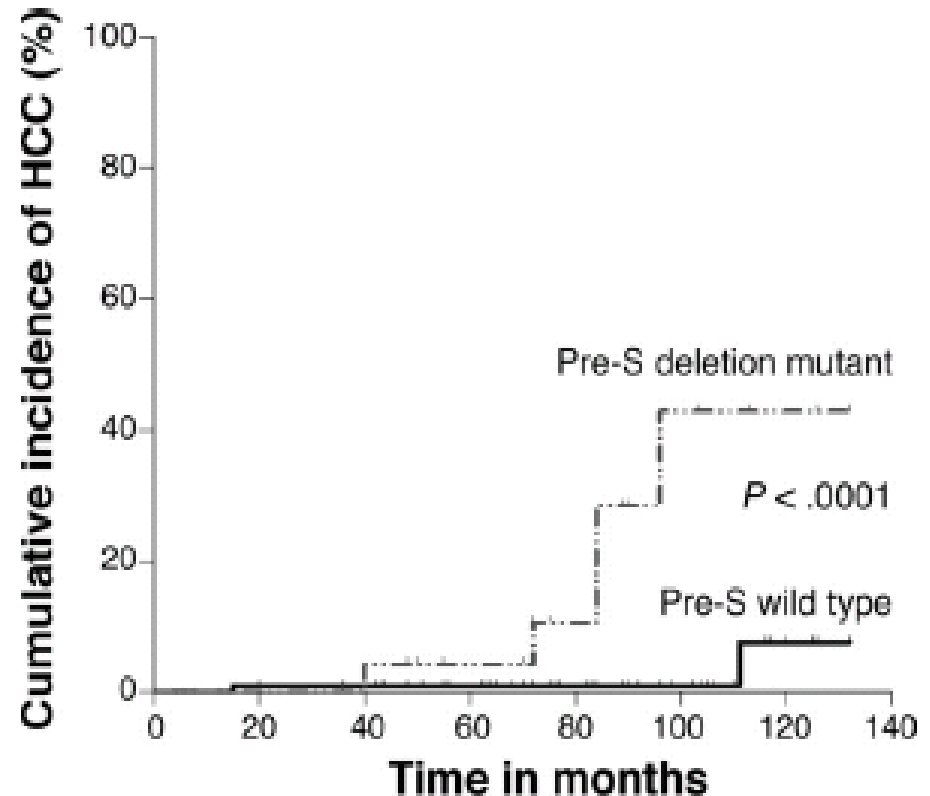
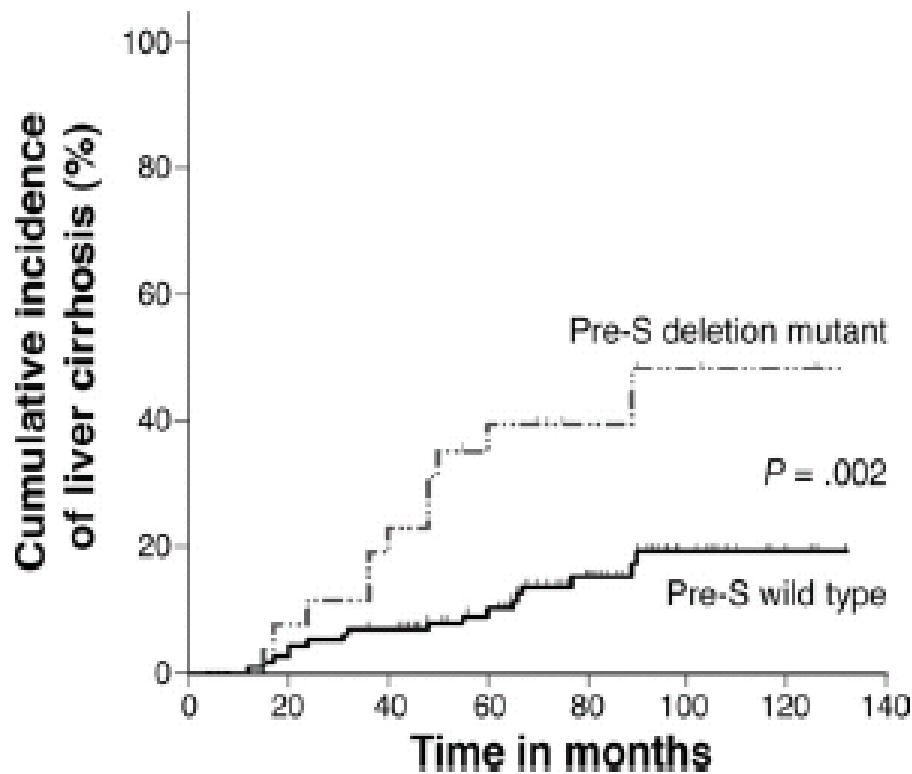
**Pre-S2 deletion mutant**

(Fan et al., 2000; Fan et al., 2001; Wang et al., 2003)

# Clinical and prognostic significance of Pre-S2 Deletion Mutations: Predict the Development of Hepatocellular Carcinoma in Chronic HBV

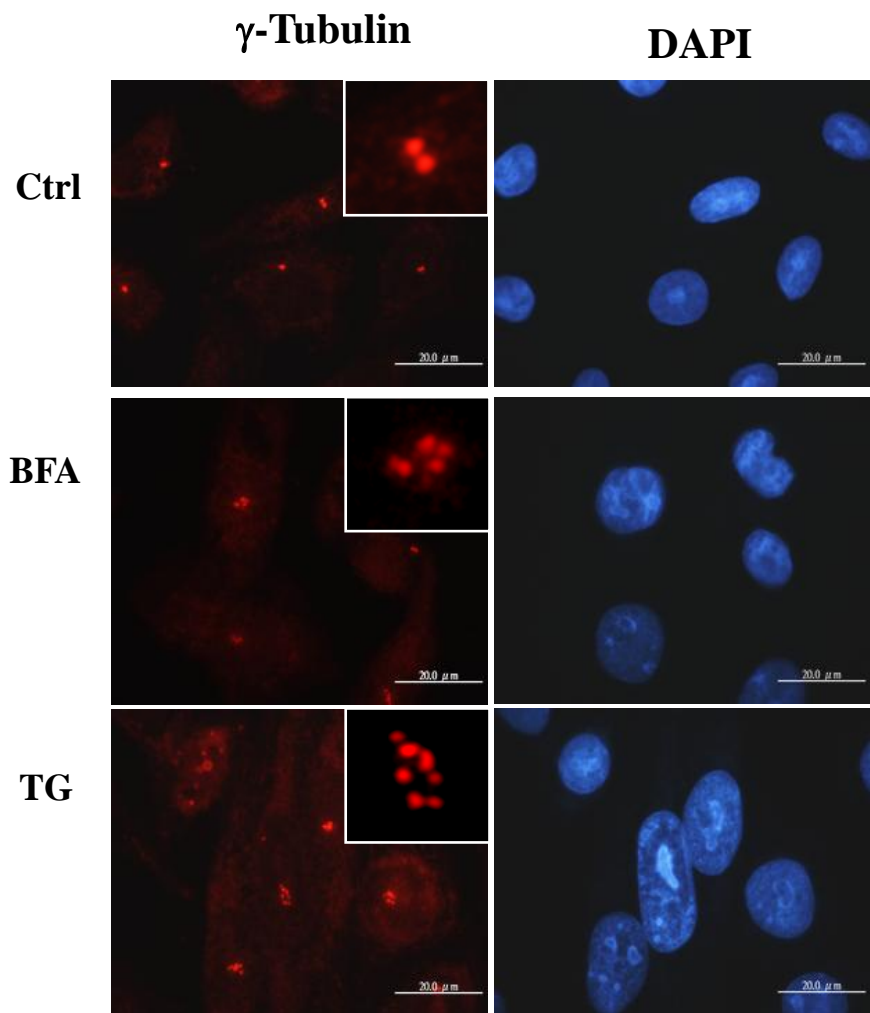
Chien-Hung Chen, et al.

*Gastroenterology*2007;133:1466

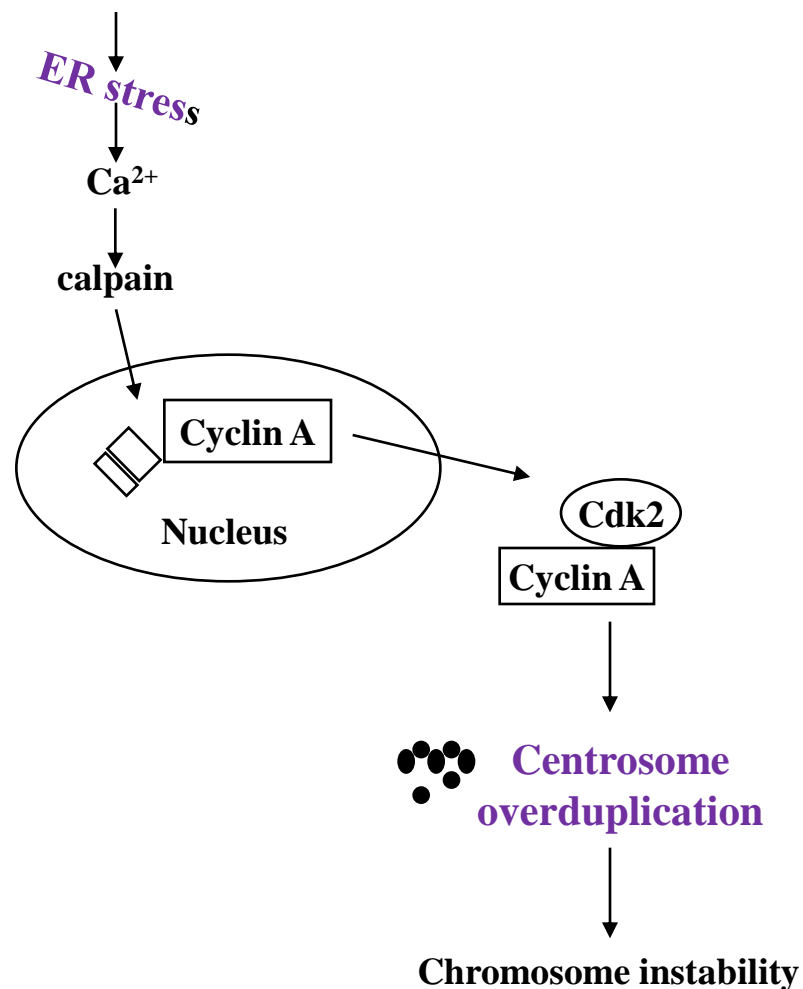


# ER stress induces cytoplasmic cyclin A and centrosome overduplication leading to genomic instability

Wang et. al., *Carcinogenesis* 2012  
Huang W, et al: *J of Pathology*, 2015

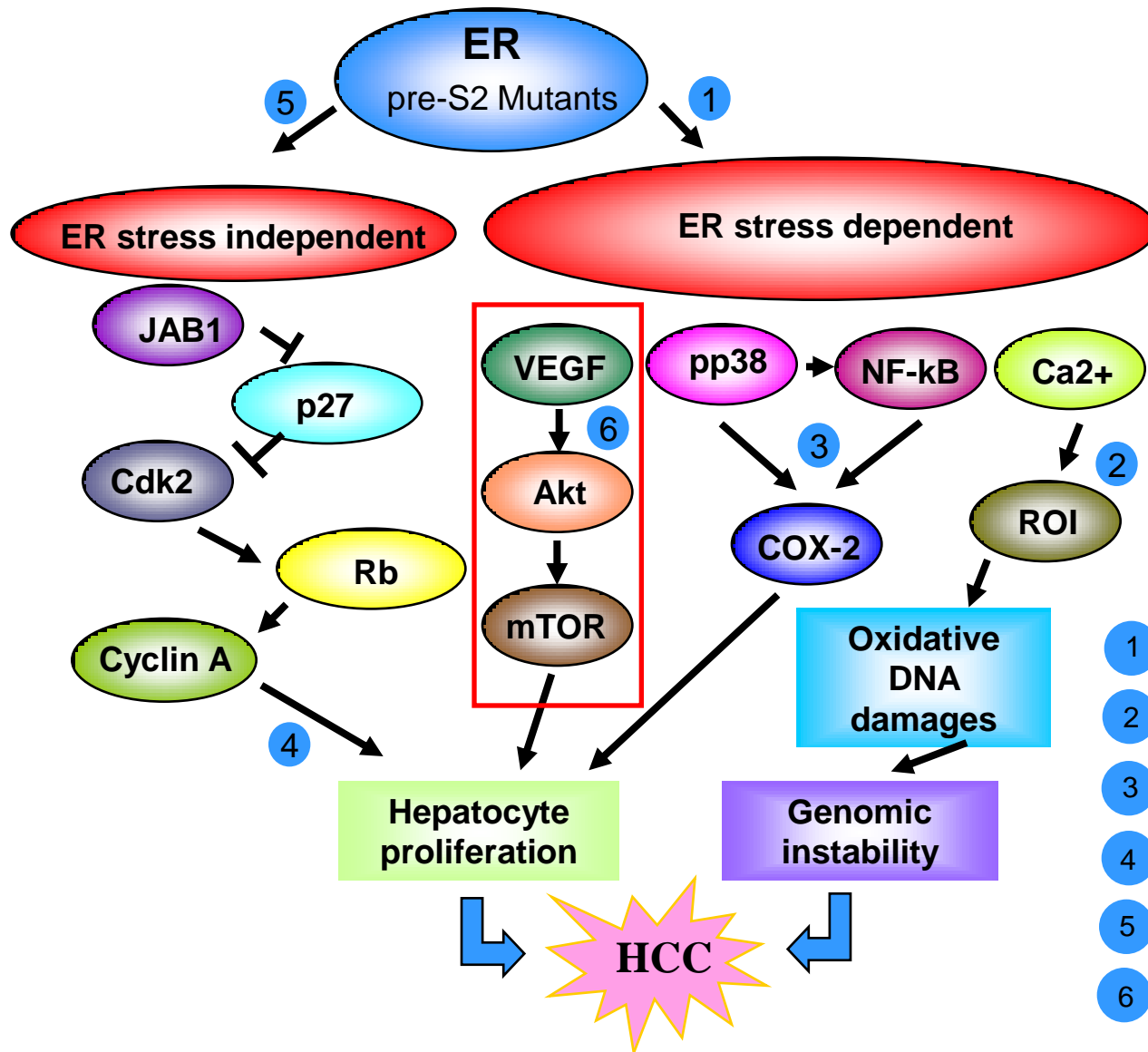


## HBV pre-S2 mutant



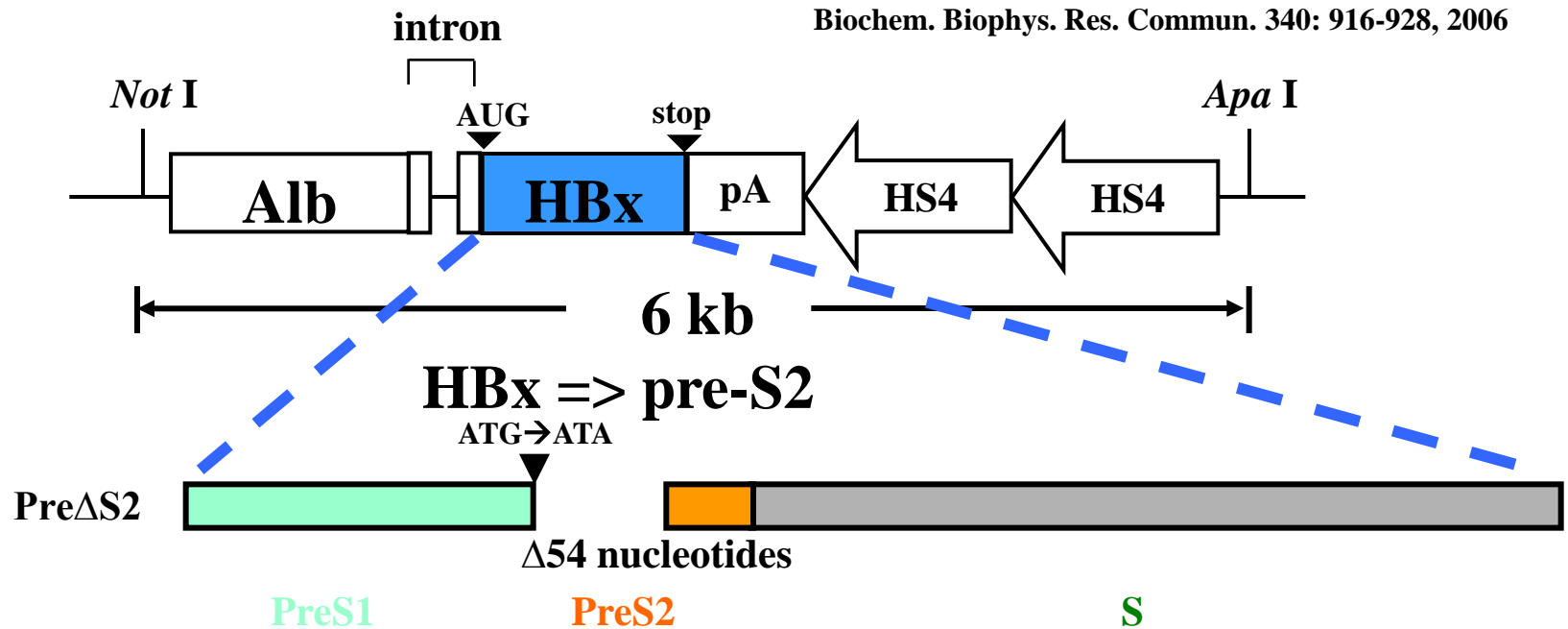


# Pre-S2 Mutants-induced ER Stress Signals in GGHs: mTOR signal cascade as key regulator for tumorigenesis



# Construction of transgenic mice model to verify the tumorigenesis by HBV pre-S2 mutants

## The Alb-Pre $\Delta$ S Transgenic Mice

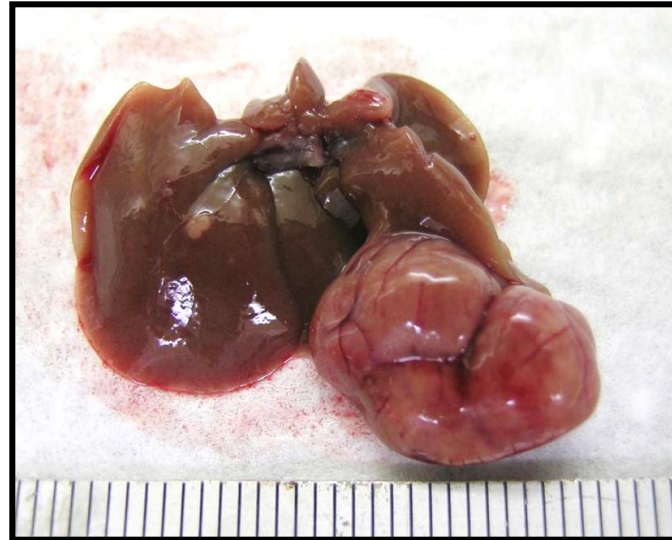


# Development of HCC in Transgenic Mice

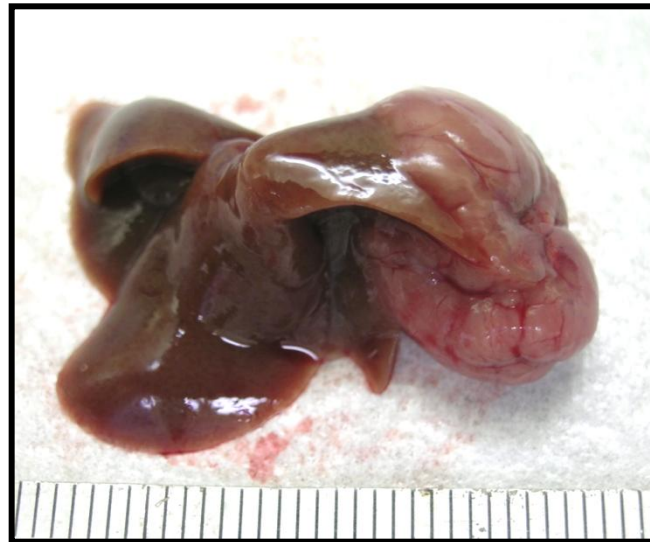
$\Delta$ S2, 22M



HBx, 16M



HBx+ $\Delta$ S2, 13M





***Metabolic Disorders in  
HBV Tumorigenesis***

***and***

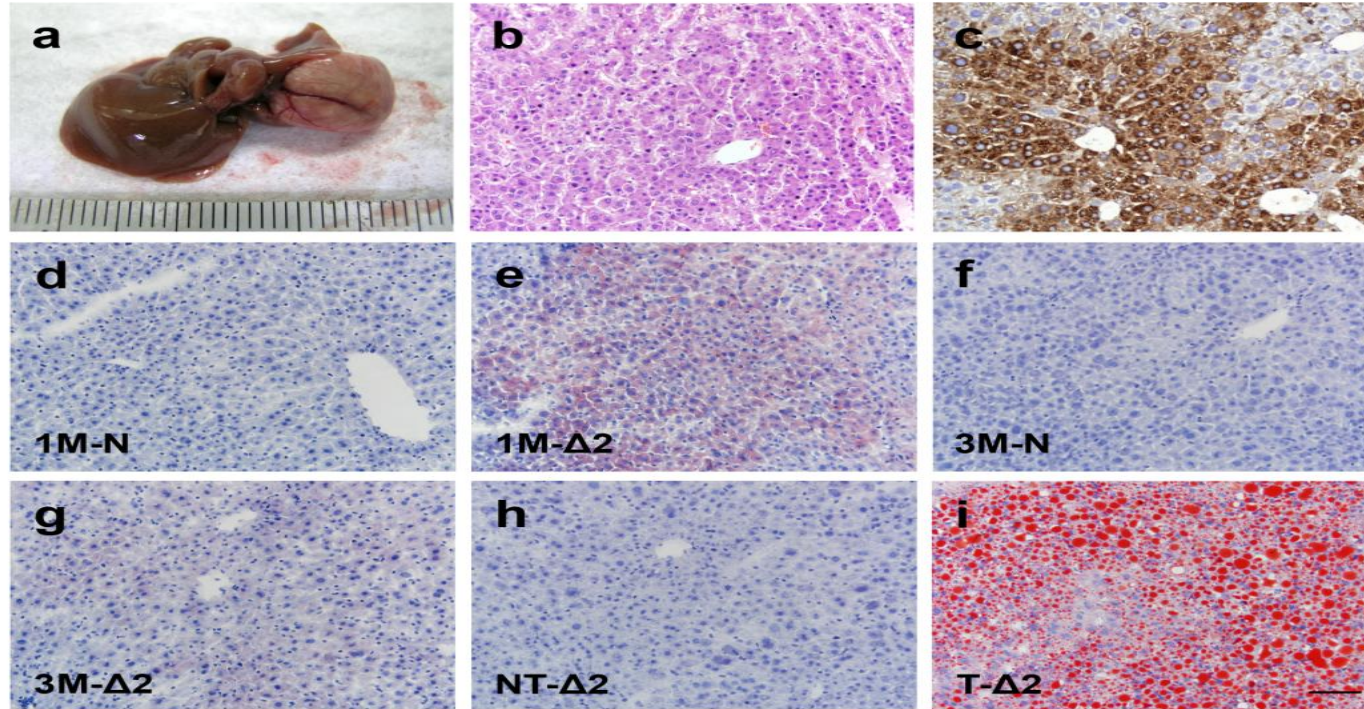
***Implication in chemoprevention in high  
risk chronic HBV patients***



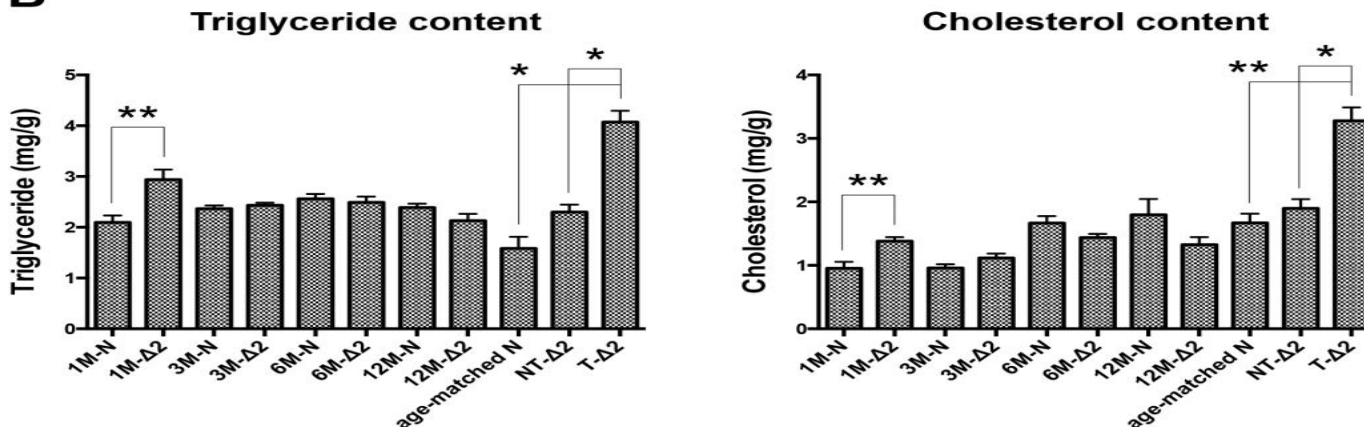


# HBV pre-S2 mutant transgenic mice exhibited increased lipid accumulation in HCC tissues: A *biphasic* pattern, early ER stress stage and terminal tumor stage

**A**



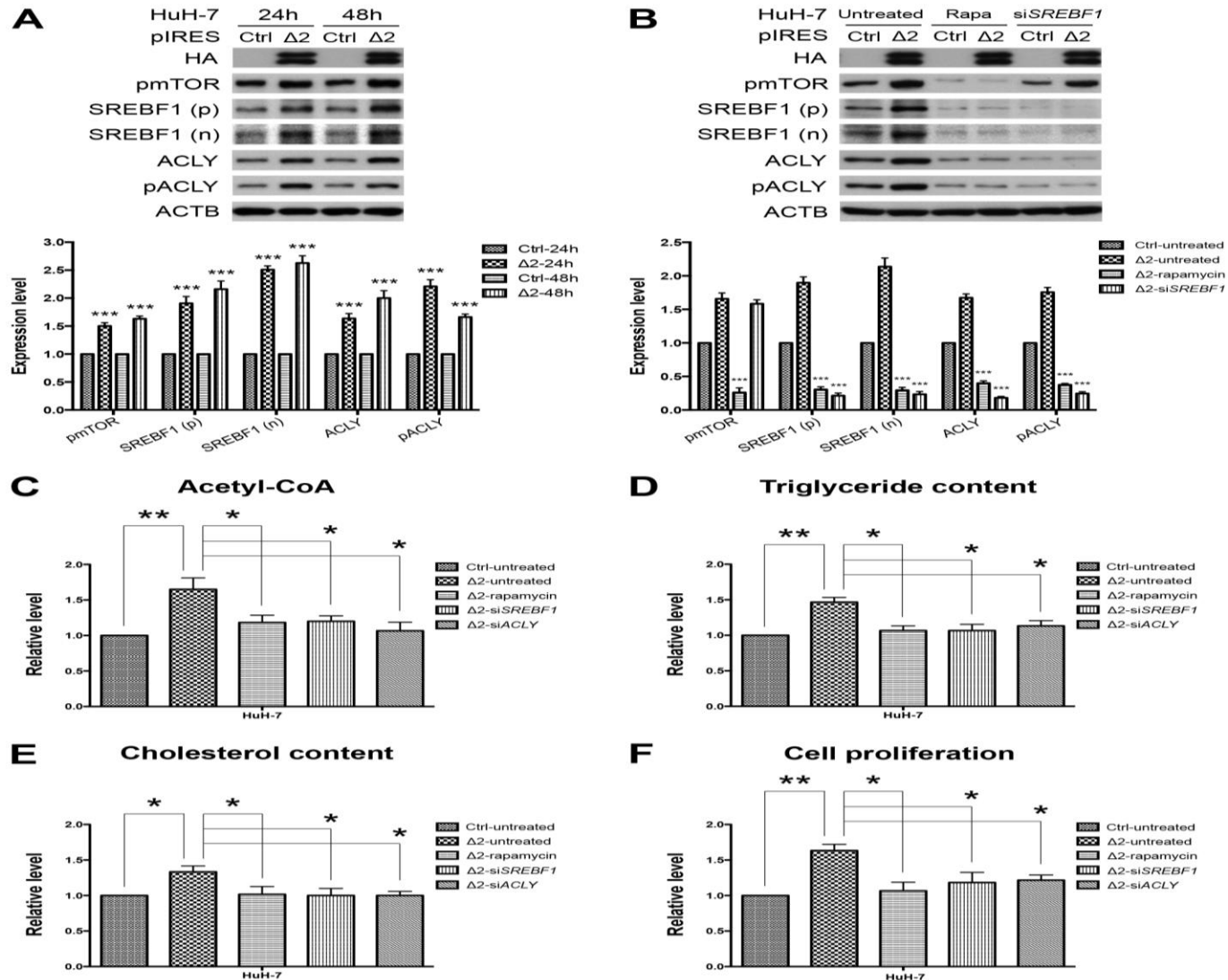
**B**



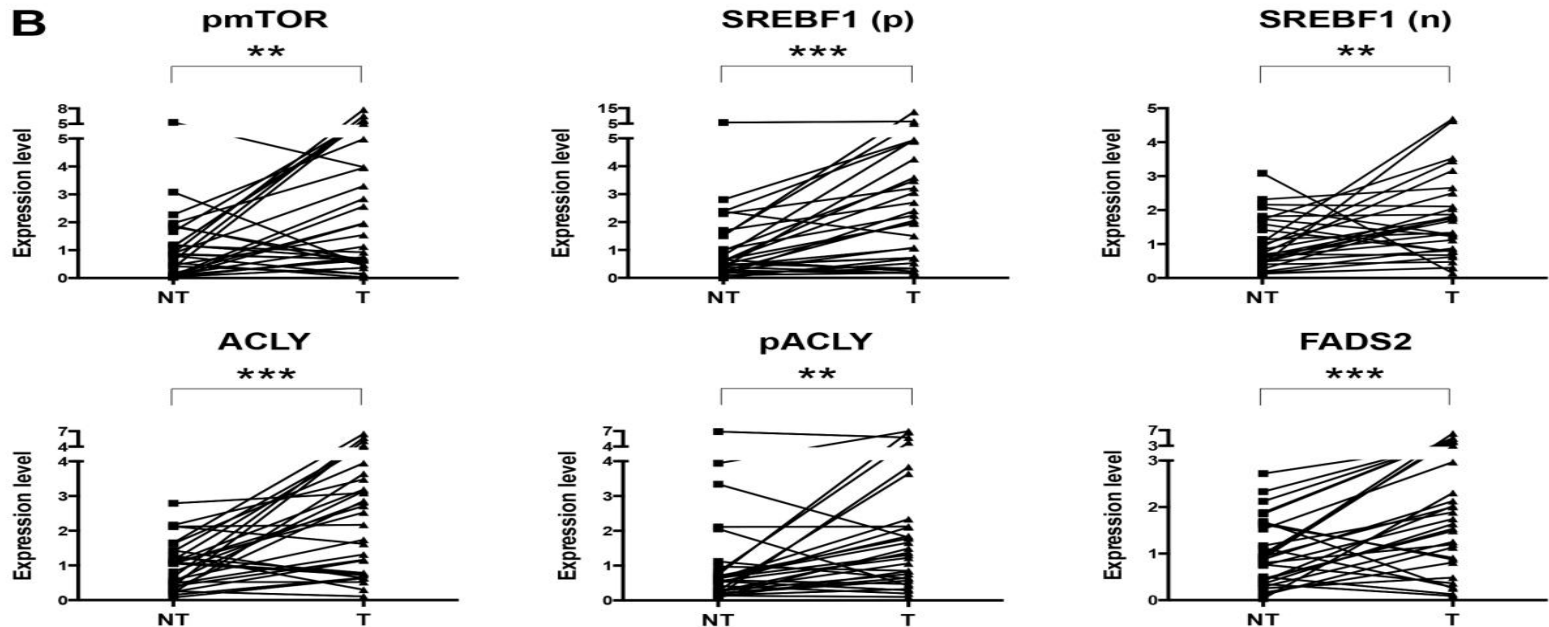
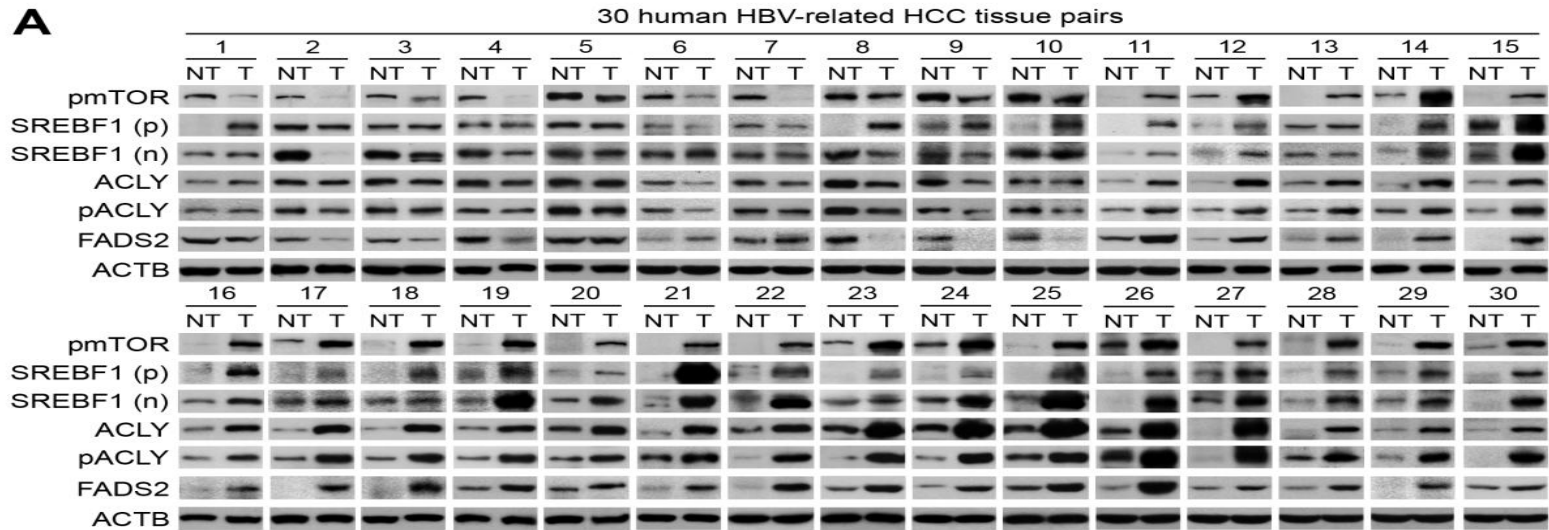




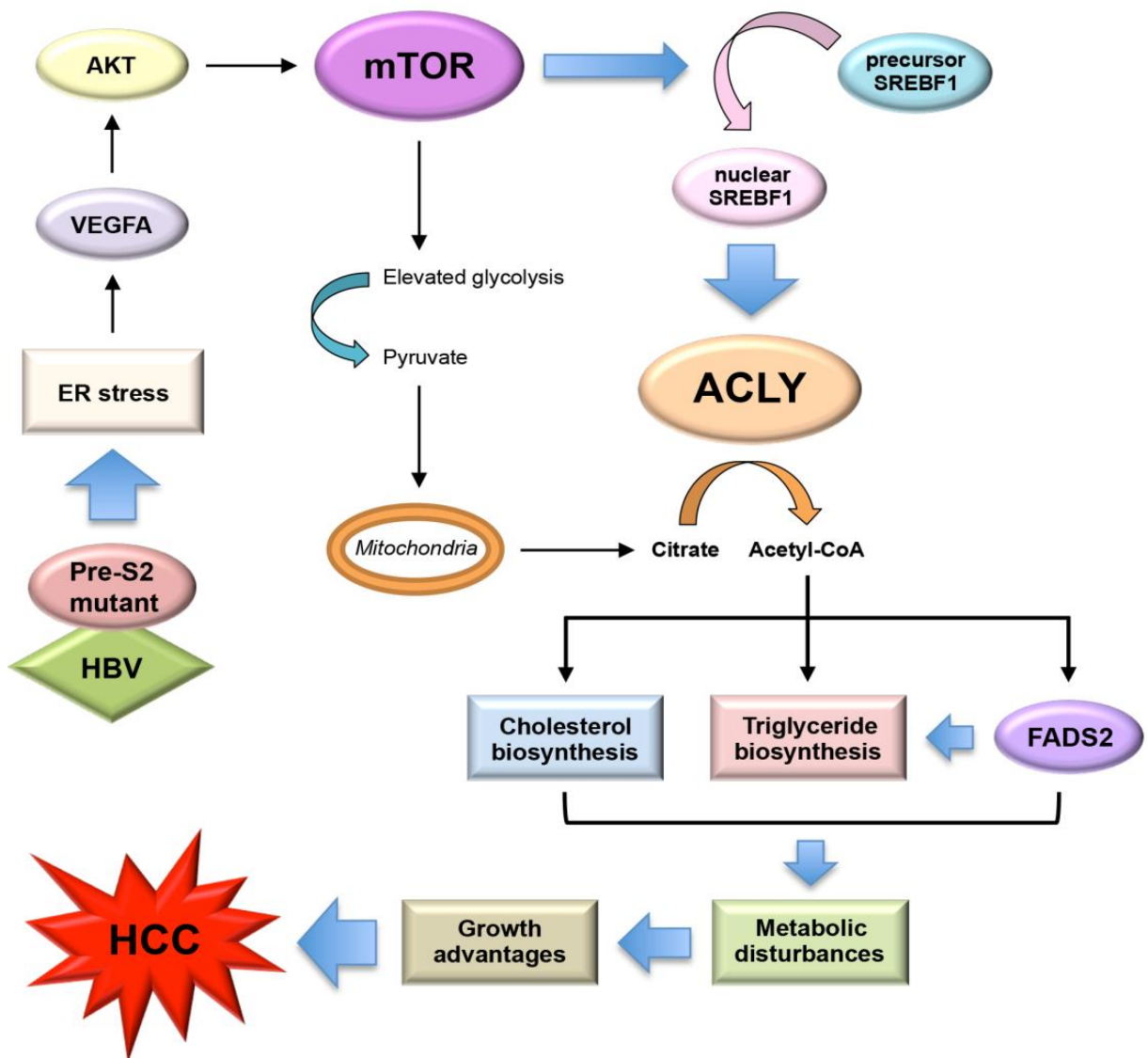
# Pre-S2 mutant activated ACLY through mTOR/SREBF1 signaling to promote de novo lipogenesis and cell proliferation in HuH-7



# The mTOR/SREBF1/ACLY/FADS2 signaling was activated in human tissues of HBV-related HCCs



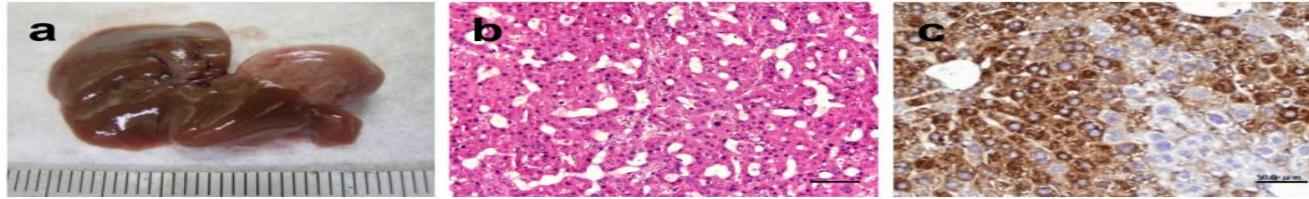
# Schematic model for the de novo lipogenesis by pre-S2 mutant in HBV tumorigenesis



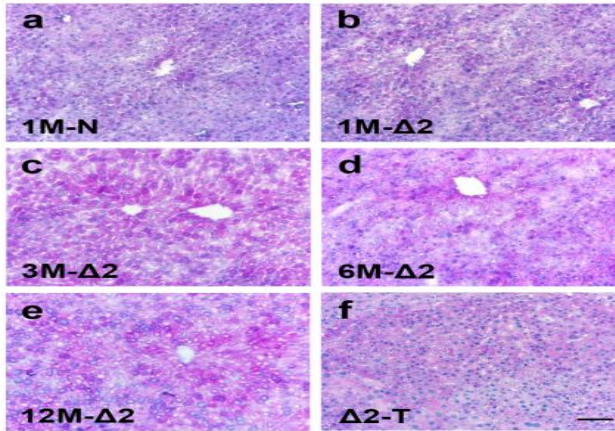


# HBV pre-S2 mutant transgenic mice exhibited **glycogen depletion** in HCC tissues, and mTOR, YY1, MYC, and SLC2A1 signals were chronologically activated

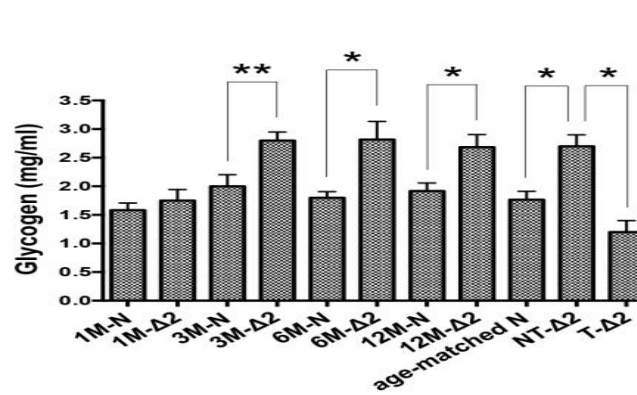
**A**



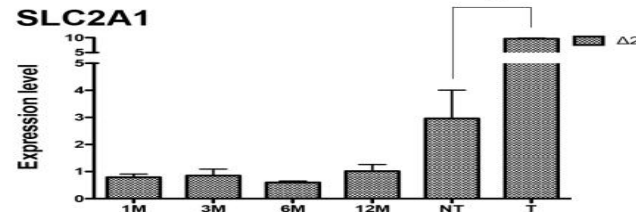
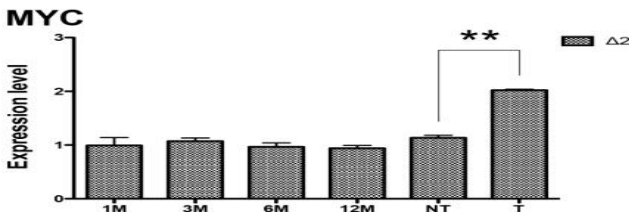
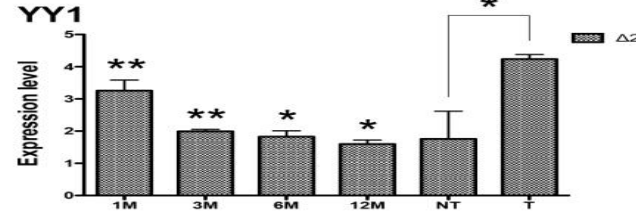
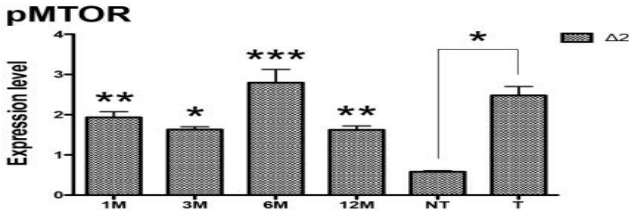
**B**



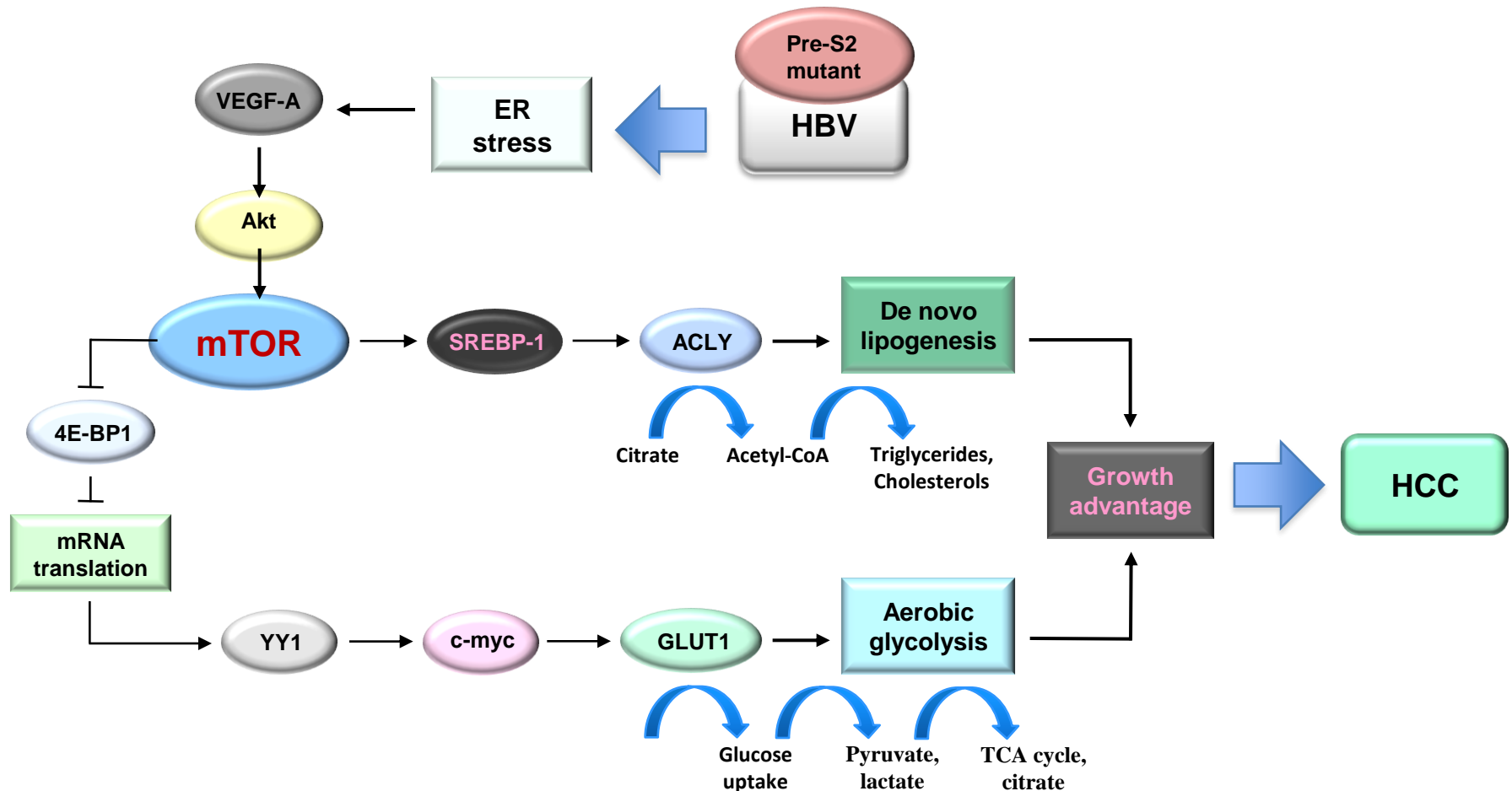
**C**



**D**



# mTOR as the key regulator of metabolomics in HBV tumorigenesis and implicates for chemoprevention

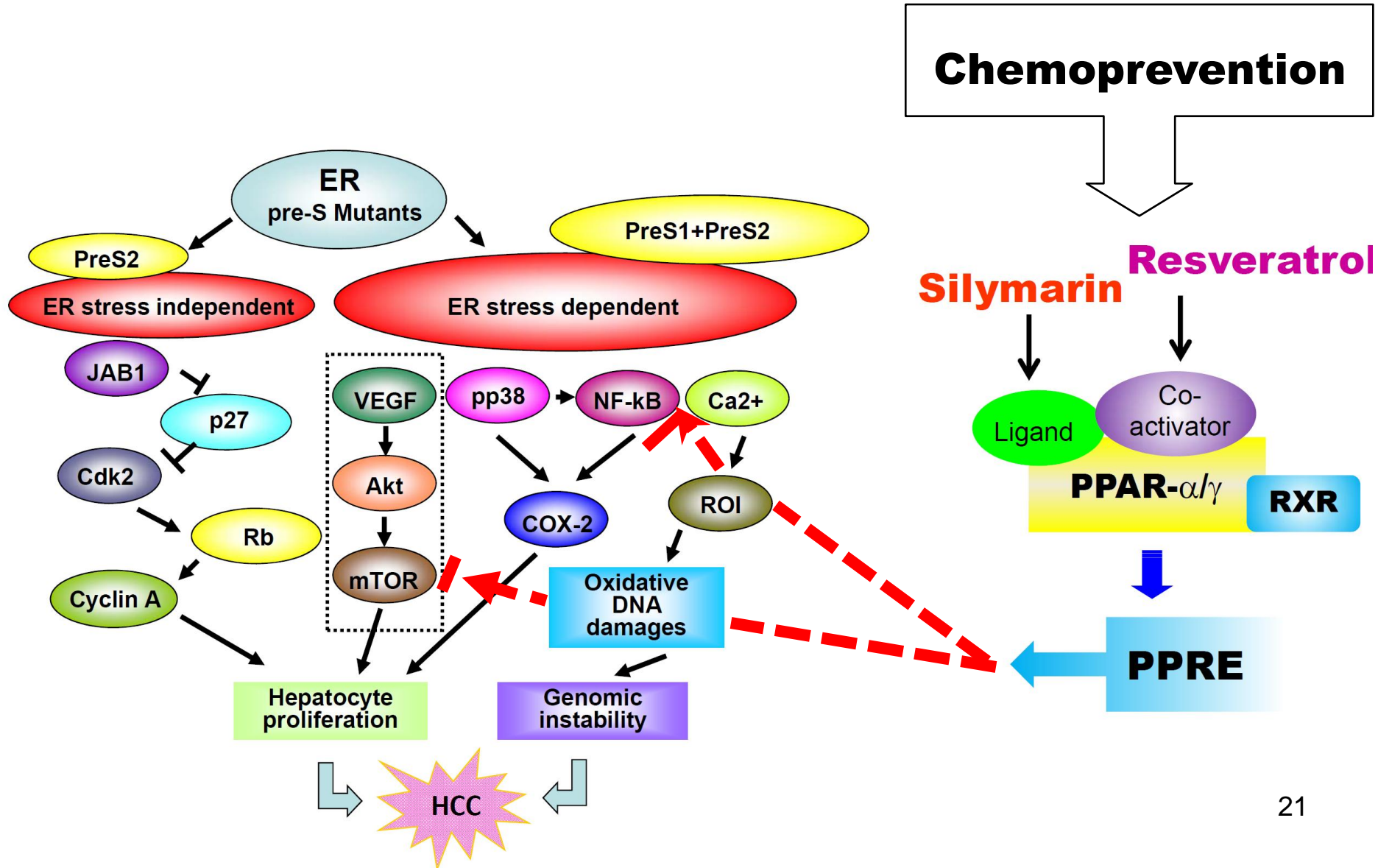


1. HBV pre-S2 mutant activated mTOR through ER stress-dependent VEGF-A/Akt signaling.
2. Activated mTOR signal upregulated YY1 through phosphorylating and inactivating 4E-BP1, a repressor of mRNA translation.
3. The YY1/c-myc/GLUT1 signaling cascade stimulated glucose uptake and aerobic glycolysis.
4. Activated mTOR signal could additionally increase ACLY expression through SREBP-1 mediation.
5. ACLY converted cytosolic citrate to acetyl-CoA, a vital building block for triglycerides and cholesterols, therefore promoting de novo lipogenesis.
6. Converged effects of aerobic glycolysis and de novo lipogenesis contributed to growth advantages of hepatocytes and HCC development.



# Proposed model for HBV chemoprevention

Targeting at **PPAR** and **mTOR** signaling pathway

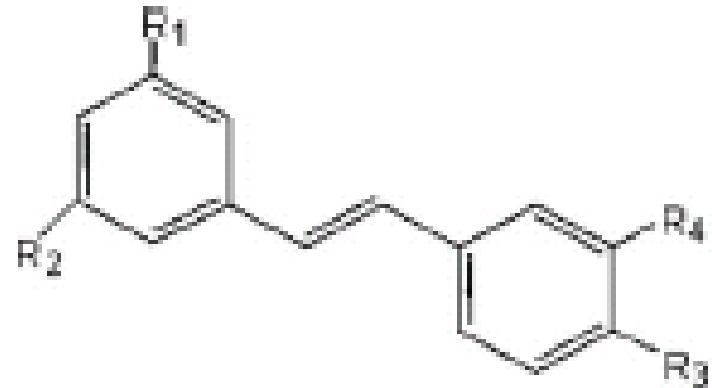


# Natural products for chemoprevention: **Resveratrol**: Red Grape Magic

- Red wine 5mg/bottle



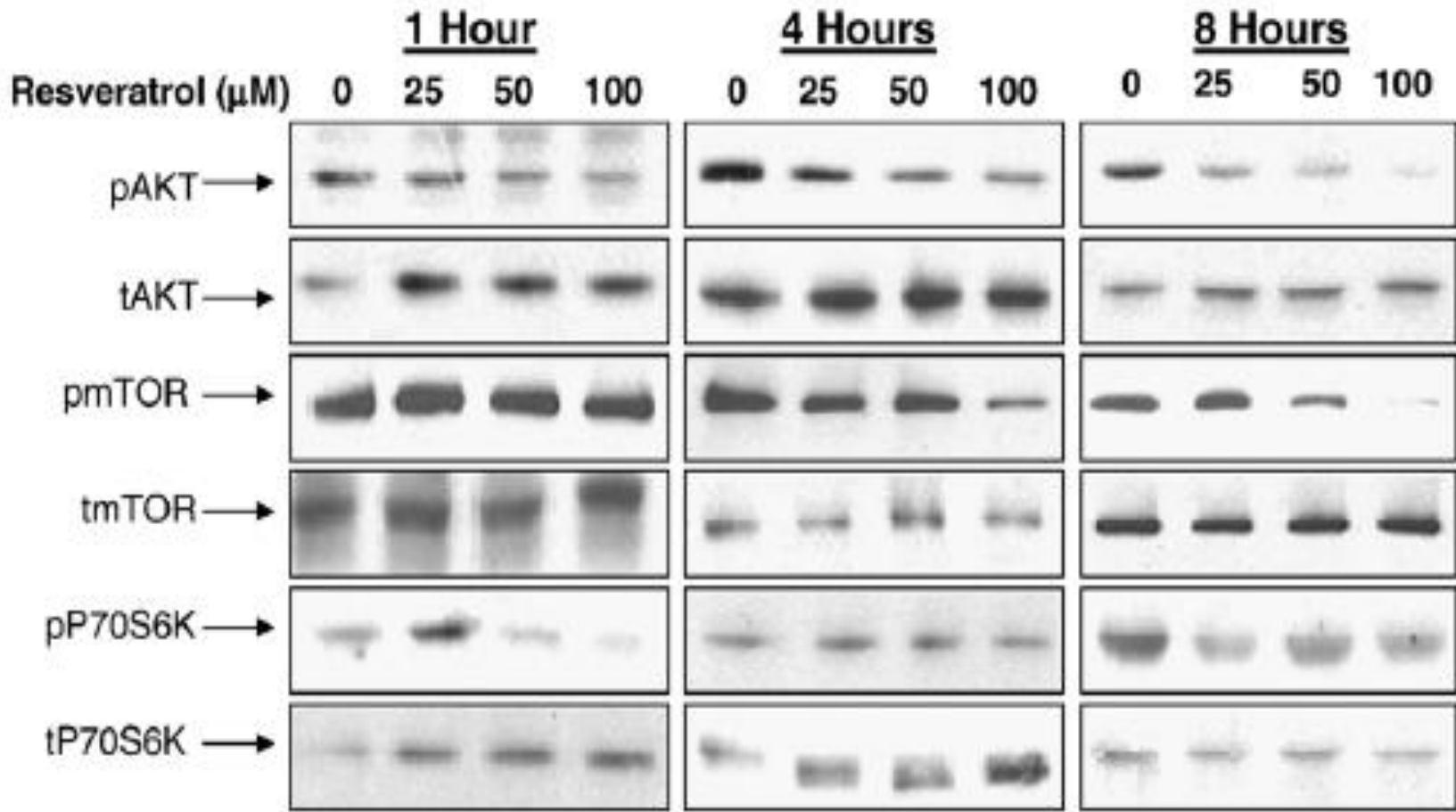
## Resveratrol



*Trans-*

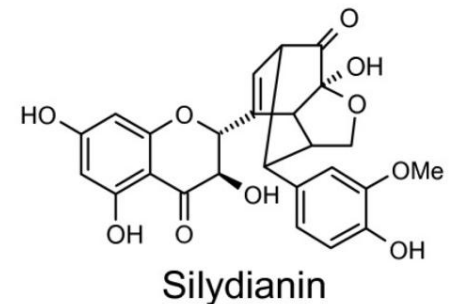
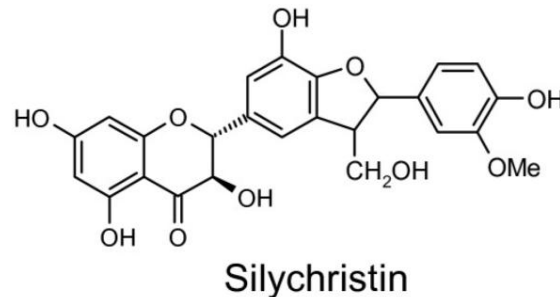
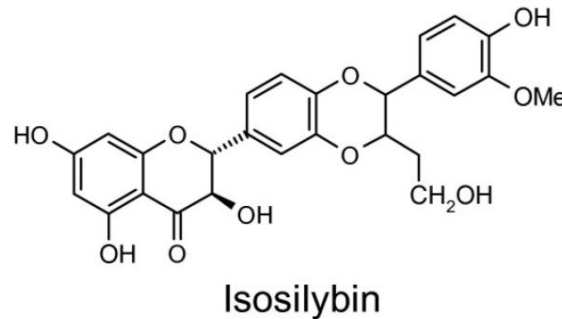
***Science* 1997: Resveratrol is effective for tumor control at the stages of tumor initiation, promotion, and prevention**

# Resveratrol ( *grape skin* ) inhibits *AKT/mTOR* signals

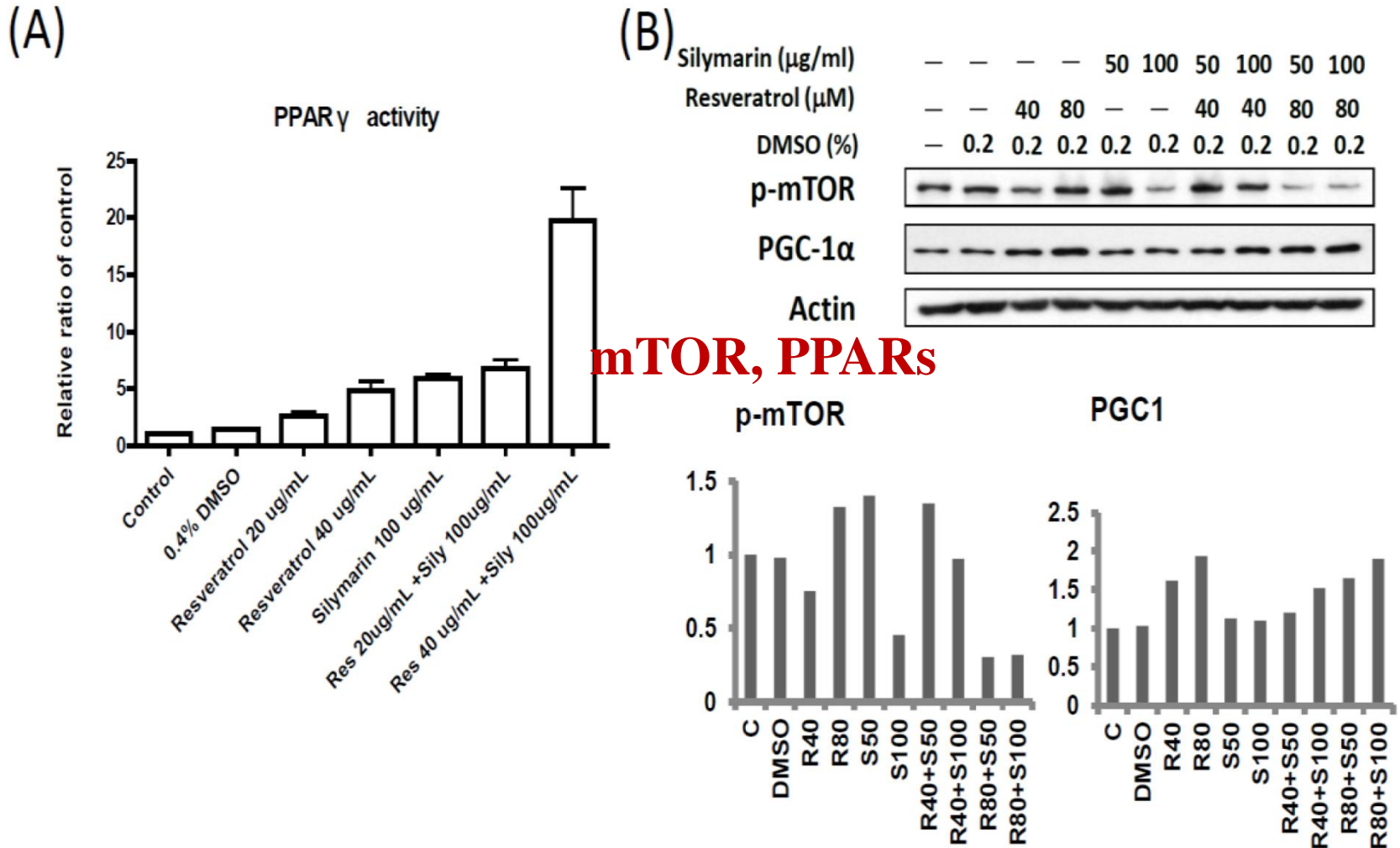


# Silymarin ( Milk thistle )

- The seed extract of *Silybum marianum* for treating liver diseases for 2000 years, now recognized as **chemopreventive and anti-cancer** agents ( *Biomedical Papers* 2005;149:29-41).
- Possess diverse pharmacological activities, including hepatoprotective, antioxidant, anti-inflammatory, anticancer, and cardioprotective.

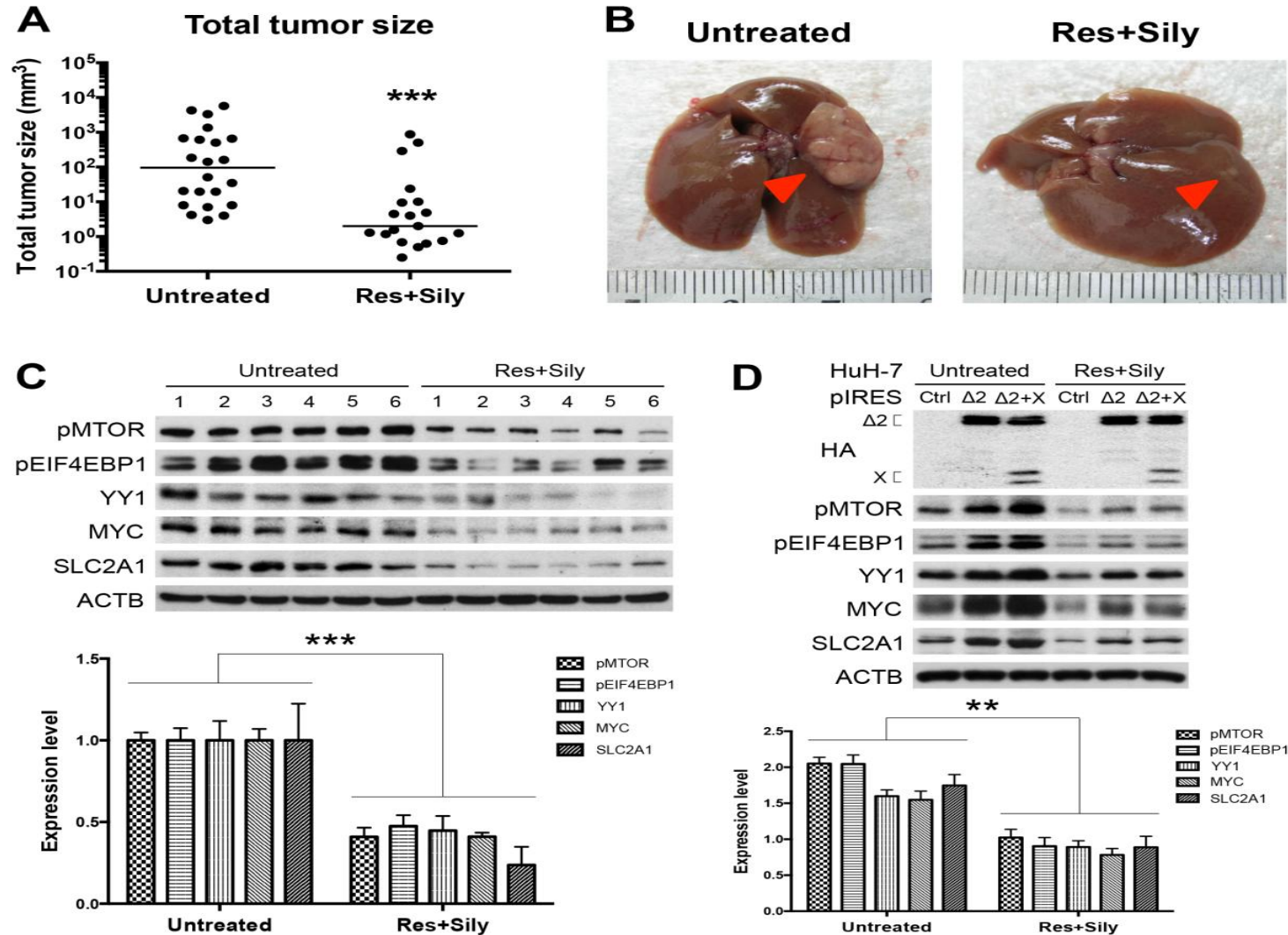


# Synergistic effect of resveratrol combined with silymarin on PPAR-g activity and p-mTOR inhibition





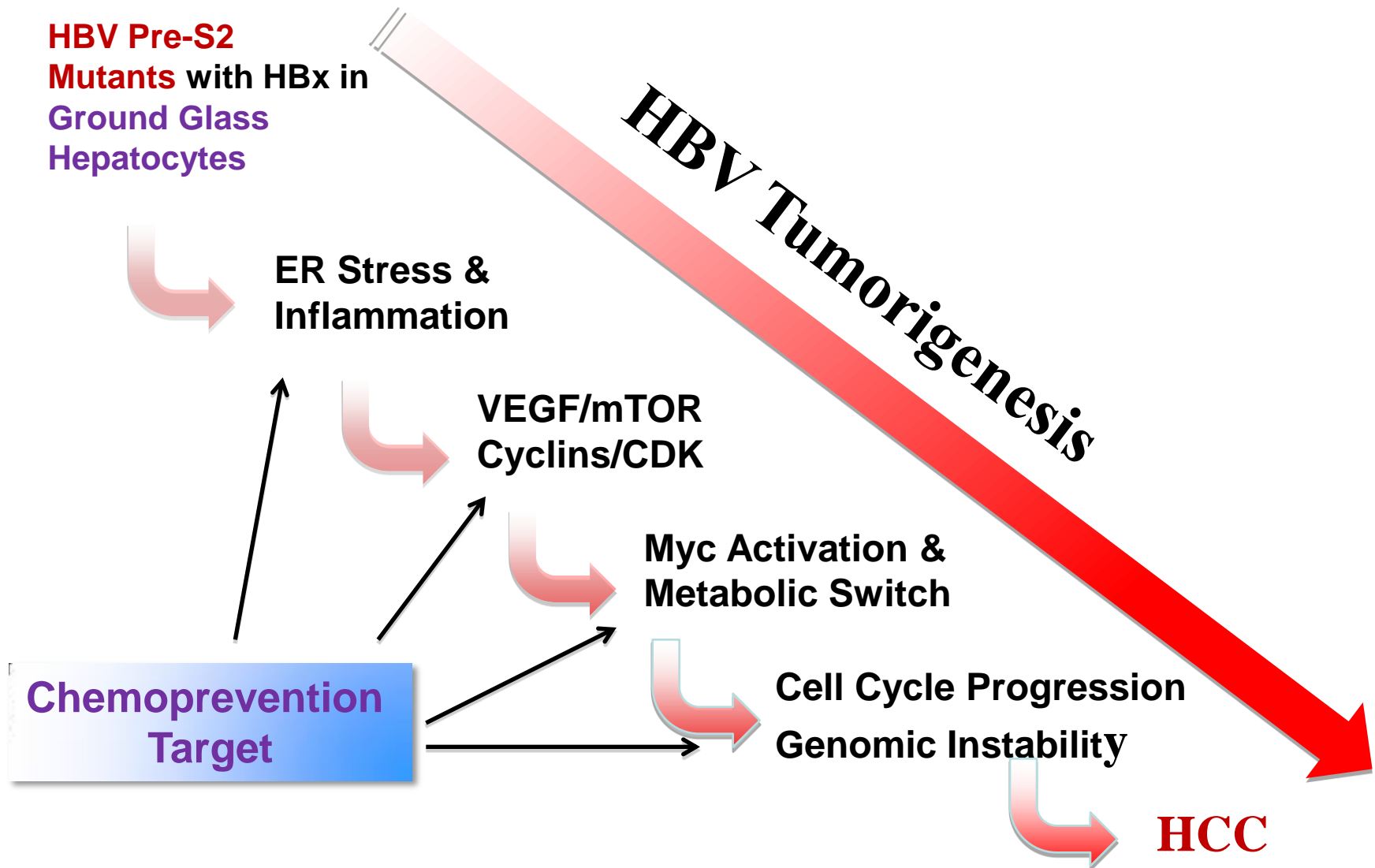
# Chemopreventive effect of combined resveratrol and silymarin product on tumor growth





# The Role of HBV Pre-S2 Mutants in HBV Tumorigenesis

**HBV Pre-S2 Mutants** with HBx in Ground Glass Hepatocytes



# Acknowledgment



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Huei-Ming Su

## National Ching-Hwa Univ..

Huei-Ching Wang

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