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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

Liaw and Chu, Lancet 2009, 373, 582-592
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

Type II GGHs

Pre-S1 deletion mutant

deletion region: 

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

\[ \gamma \text{-Tubulin} \quad \text{DAPI} \]

- Ctrl
- BFA
- TG

HBV pre-S2 mutant

\[ \text{ER stress} \rightarrow \text{Ca}^{2+} \rightarrow \text{calpain} \]

Cyclin A

Nucleus

Cdk2

Centrosome overduplication

Chromosome instability

Wang et. al., Carcinogenesis 2012
Huang W, et al: J of Pathology, 2015
Pre-S2 Mutants-induced ER Stress Signals in GGHs: mTOR signal cascade as key regulator for tumorigenesis

ER stress independent

ER stress dependent

JAB1
p27
Cdk2
Rb
Cyclin A

VEGF
Akt
mTOR

pp38
NF-kB
Ca2+
COX-2
ROI

Oxidative DNA damages

Hepatocyte proliferation

Genomic instability

HCC

1. Wang HC et al., 2003
2. Hsieh YH et al., 2004
3. Hung JH et al., 2004
4. Wang HC et al., 2005
5. Hsieh YH et al., 2007
6. Yang JC et al., 2009
Construction of transgenic mice model to verify the tumorigenesis by HBV pre-S2 mutants

The Alb-PreΔS Transgenic Mice


PreΔS2

△54 nucleotides

PreS1  PreS2  S
Development of HCC in Transgenic Mice

ΔS2, 22M

HBx, 16M

HBx+ΔS2, 13M
Metabolic Disorders in HBV Tumorigenesis and Implication in chemoprevention in high risk chronic HBV patients
cDNA microarray to explore the expression profiles of metabolic genes in HBV pre-S2 mutant-transgenic mice livers and tumors

(modified from Gaschwind DH et al., 2003)
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

Triglyceride content

Cholesterol content
mTOR, ACLY, and SREBF1 signals were chronologically activated in pre-S2 mutant transgenic livers and HCCs: biphasic pattern for mTOR and ACLY
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.
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

Chemoprevention

Silymarin

Resveratrol

PPAR-α/γ

PPRE

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

- Red wine 5mg/bottle

**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-γ 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

ER Stress & Inflammation

VEGF/mTOR Cyclins/CDK

Myc Activation & Metabolic Switch

Cell Cycle Progression Genomic Instability

Chemoprevention Target

HCC
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