

The background of the slide is a grayscale electron micrograph of a mitochondrion. It shows a network of cristae, which are the internal folds of the mitochondrial membrane, arranged in a somewhat circular or oval pattern. The cristae are closely packed and appear as dark, wavy lines against a lighter background.

# **Mitochondrially-localized Parkin and Its Role in Innate Immune Response**

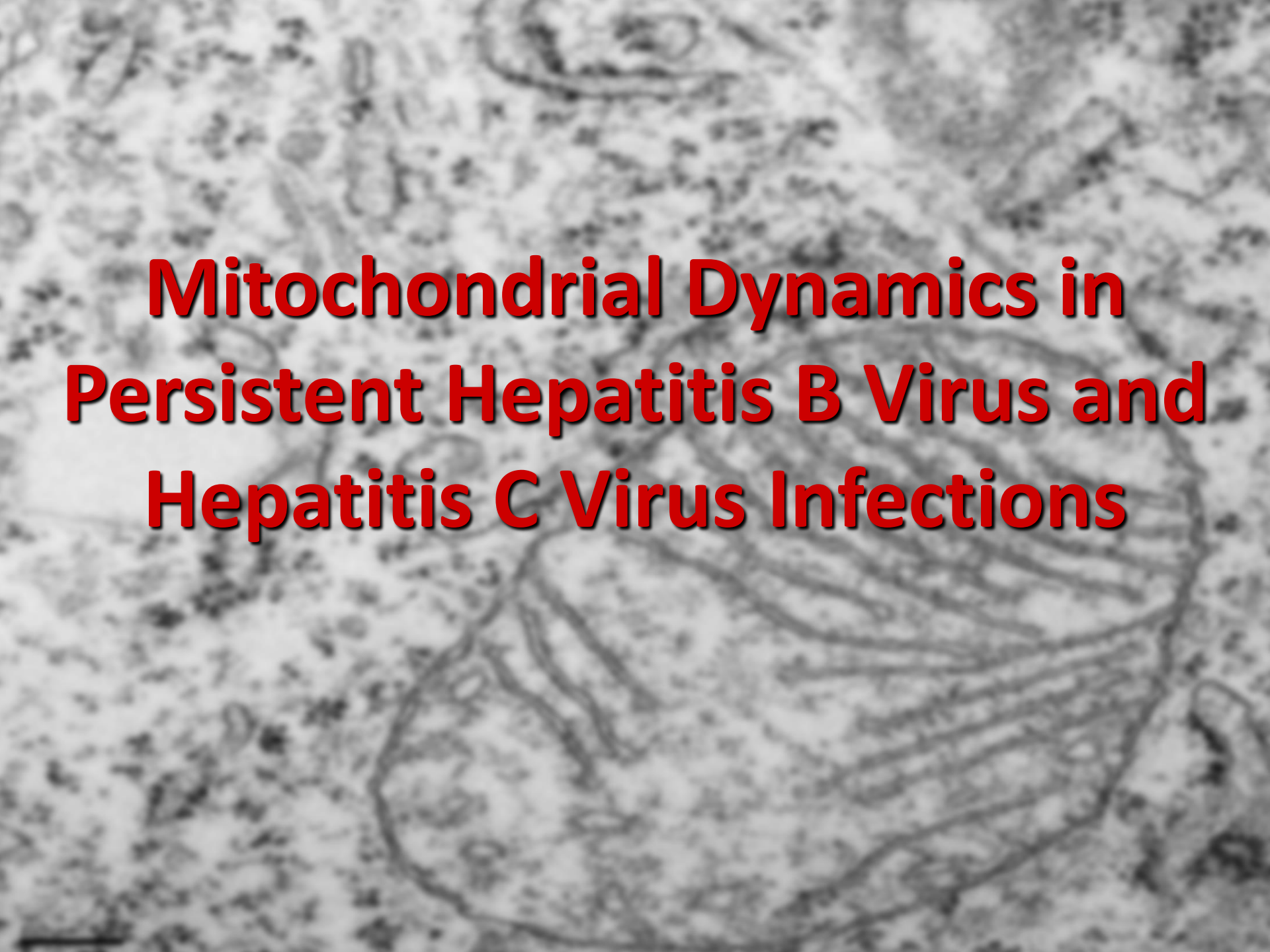
**Seong-Jun Kim**

Principal Researcher

Center for Virus Research and Testing

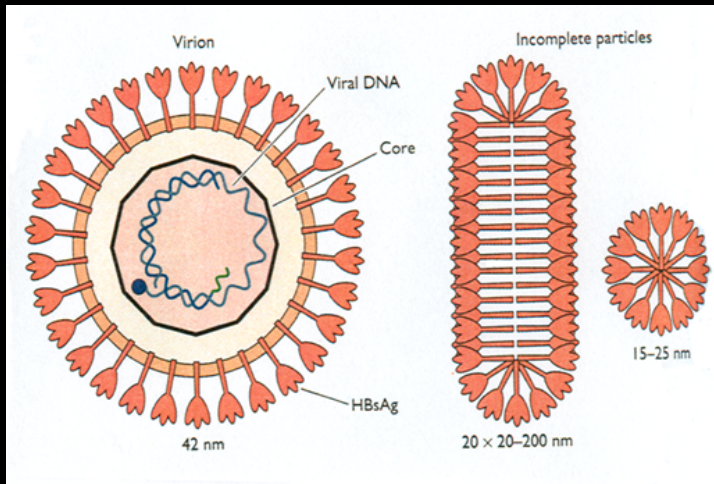
Division of Bio & Drug Discovery

Korea Research Institute of Chemical Technology

An electron micrograph showing a large, roughly circular mitochondrion with a highly folded inner membrane (cristae) and a granular matrix. The background shows other cellular structures, including smaller organelles and cytoplasmic components.

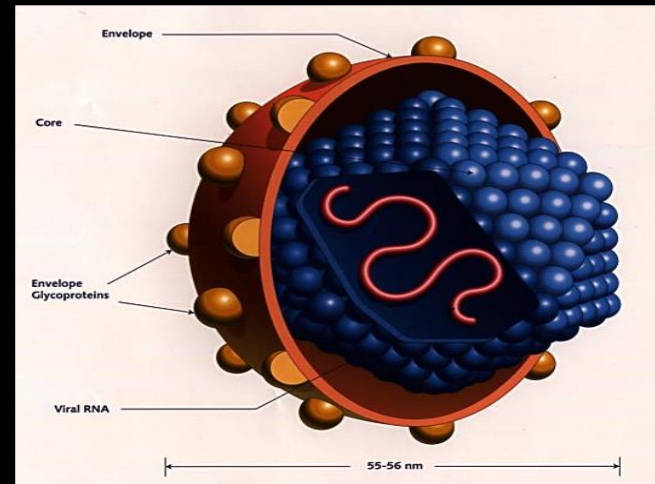
**Mitochondrial Dynamics in  
Persistent Hepatitis B Virus and  
Hepatitis C Virus Infections**

# Hepatitis B Virus (HBV)



- *Hepadnavirus* family
- Enveloped **DNA virus**
- DNA genome which encodes 4 overlapping ORF:
  - pre-S/S (surface antigen)
  - C (core/e antigen)
  - P (polymerase, reverse transcriptase)
  - X (HBx)

# Hepatitis C Virus (HCV)

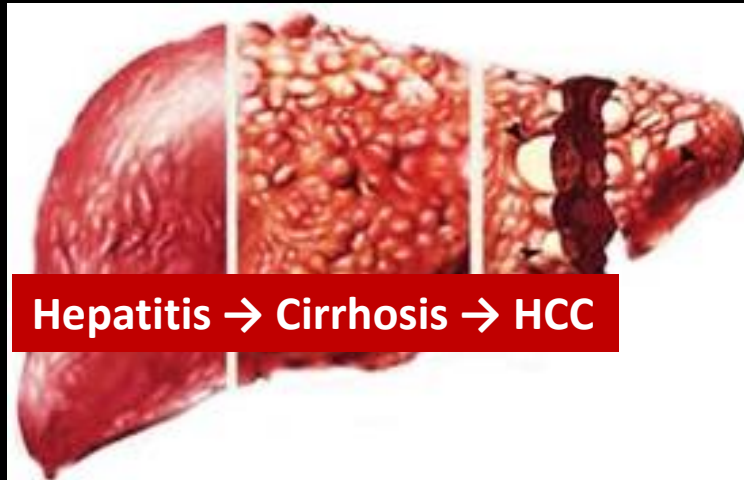


- *Flaviviridae* family
- Enveloped **RNA virus**
- positive strand RNA genome which encodes single polyprotein precursor that post-translationally produces:
  - 4 mature structural proteins
  - 6 mature nonstructural proteins

# HBV & HCV Cause Similar Pathogenesis of Liver

- Hepatitis A virus (HAV)
- **Hepatitis B virus (HBV)** →
- **Hepatitis C virus (HCV)** →
- Hepatitis D virus (HDV, Delta agent)
- Hepatitis E virus (HEV)
- Hepatitis G virus (HGV)

*Blood-borne  
Chronic hepatitis  
Hepatocellular carcinoma*



## HBV & HCV Induce various cellular & physiological alterations:

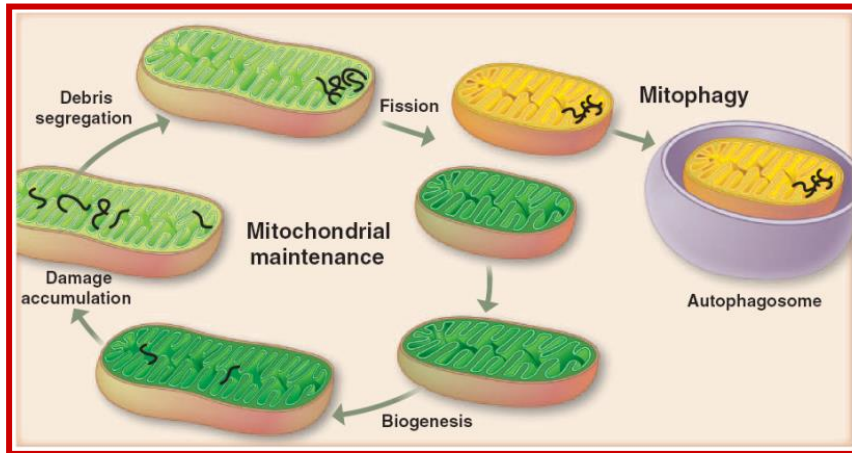
- ER stress, ER Ca<sup>2+</sup> depletion
- ROS generation: high
- Mitochondrial membrane potential: low
- Mitochondrial depolarization & swelling
- Impairment in  $\beta$ -oxidation

*: Associated with chronic liver Diseases*

***HBV & HCV***

***Induce Mitochondrial Fission***

# Mitochondrial dynamics

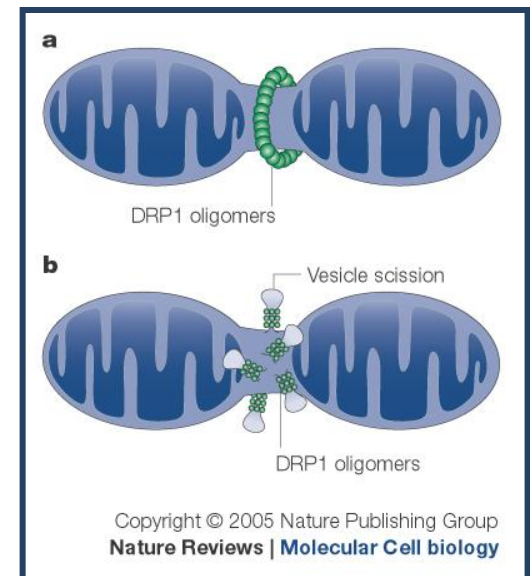


- Mitochondrial dynamics : involves fission, fusion, and mitophagy
- Mitochondrial fusion  
: In healthy cells, mitochondria  
1) fuse to form tubular network  
2) conserve energy
- Fusion factors: Mitofusin 1/2 and Opa1

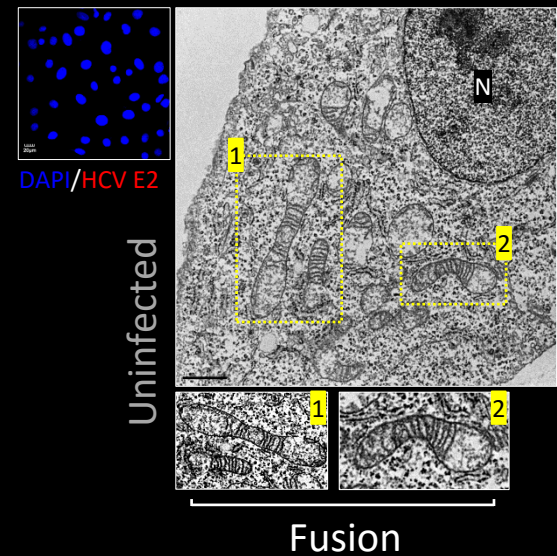
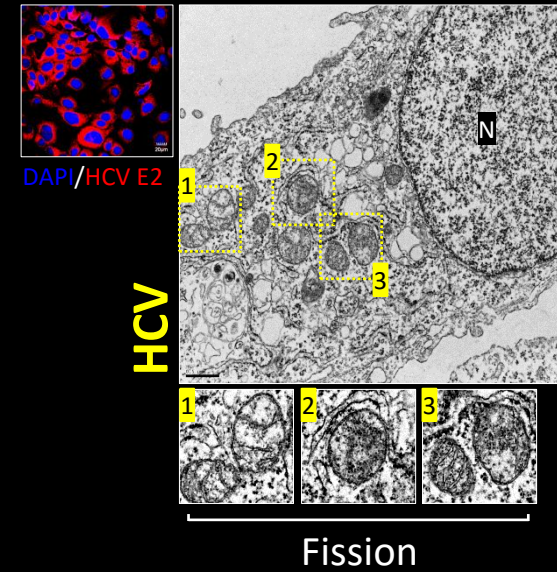
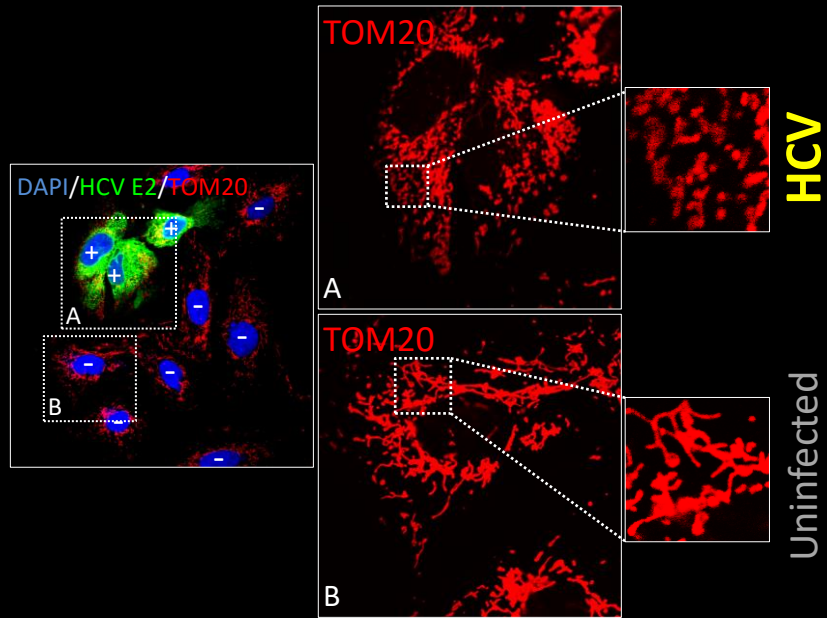
- Mitochondrial fission

- 1) Is a general stress response of cells
- 2) Contributes mitochondrial quality control in stressed cells
- 3) is the mechanism to segregate healthy and damaged mitochondria
- 4) is initiated by activation of Drp1 by Ser616 phosphorylation leading to mitochondrial translocation (Fission factor: Drp1)

- Drp1 receptor: Mitochondrial fission factor (Mff)



# HCV: *Induces Mitochondrial Fission*

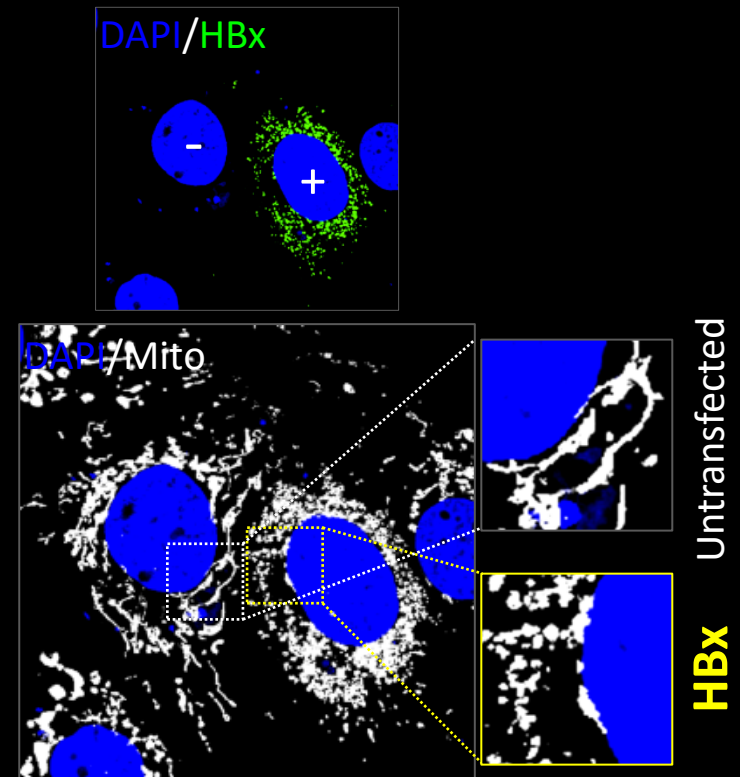
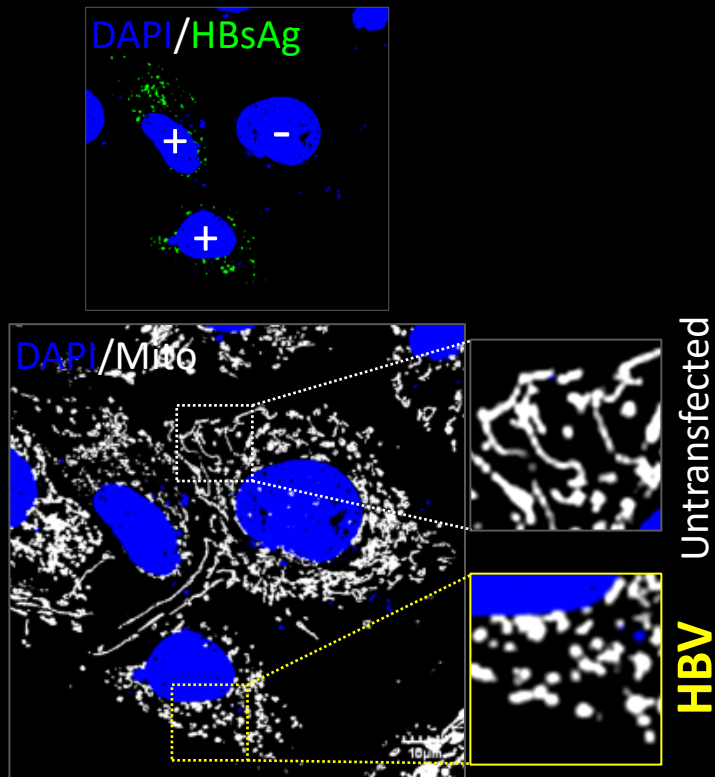




# HBV/HBx: *Induces Mitochondrial Fission*

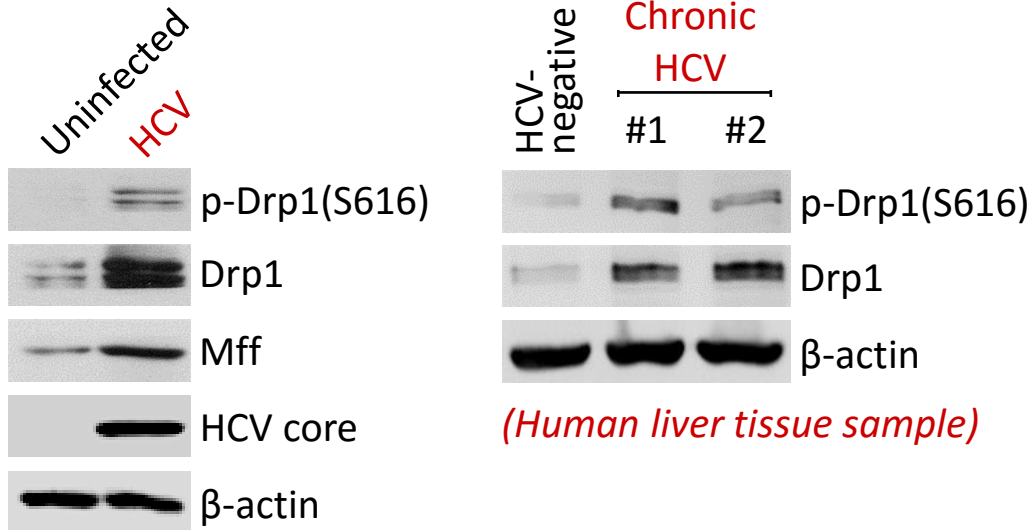
*HBV whole genome expression*

*HBx expression*

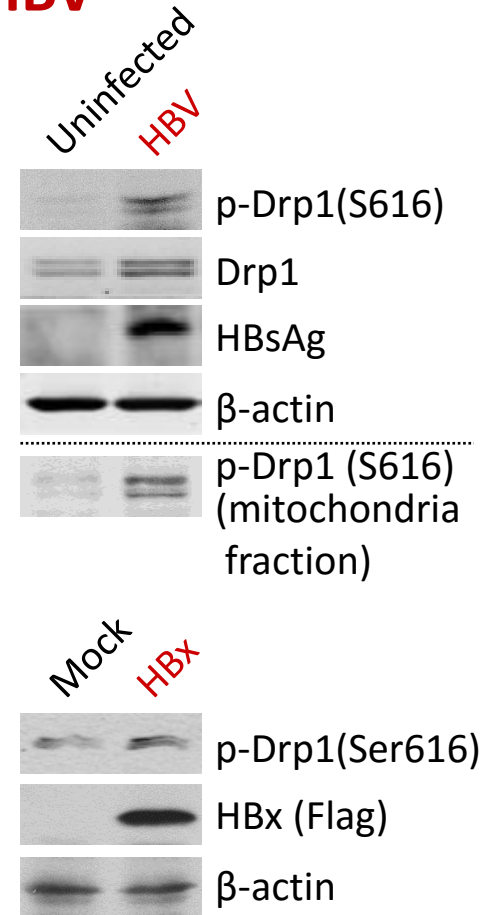


# HBV & HCV: Stimulates Drp1 Expression and Its Ser616 Phosphorylation

## HCV



## HBV

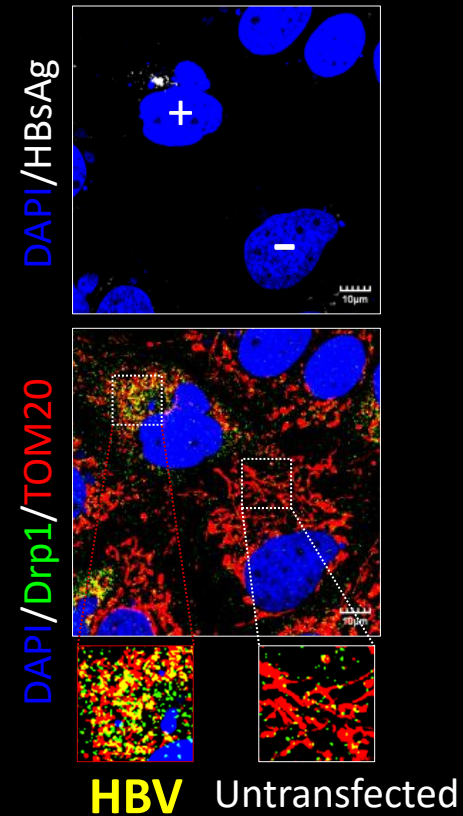
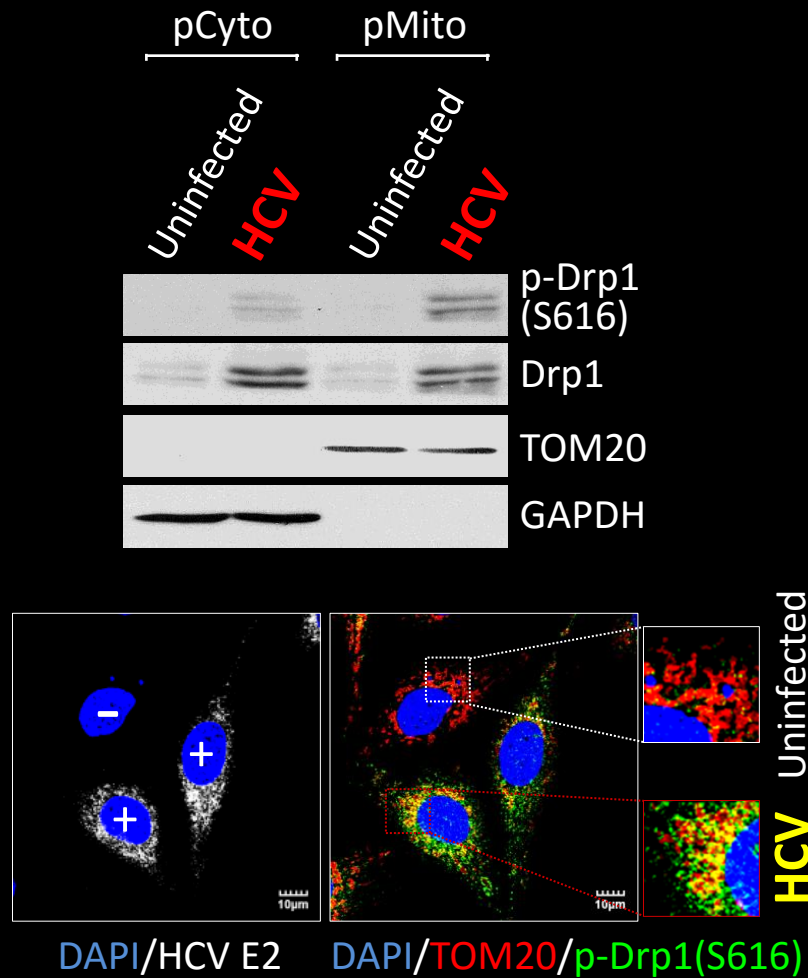


Kim et al, PLoS Pathog, 2013, 12: e1003722

Kim et al, PLoS Pathog, 2013, 3:e1003285

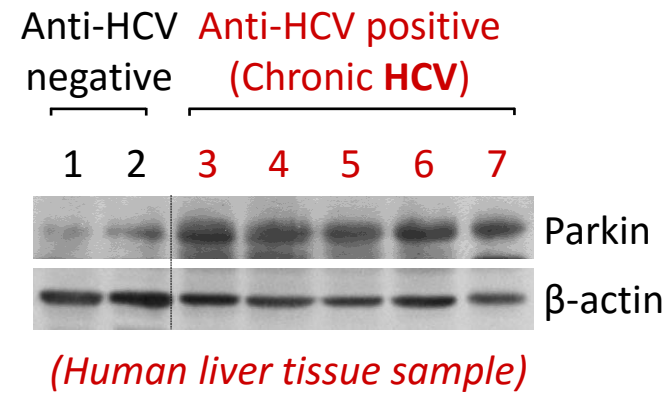
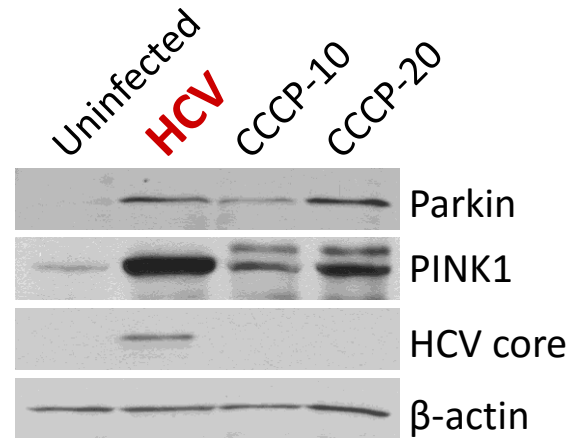
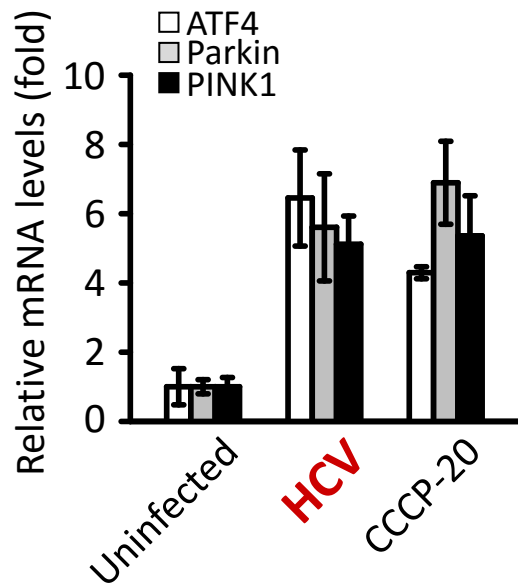
Kim et al, PNAS, 2014, 111:6413-6418

# HBV & HCV: Induces Drp1 Translocation to Mitochondria



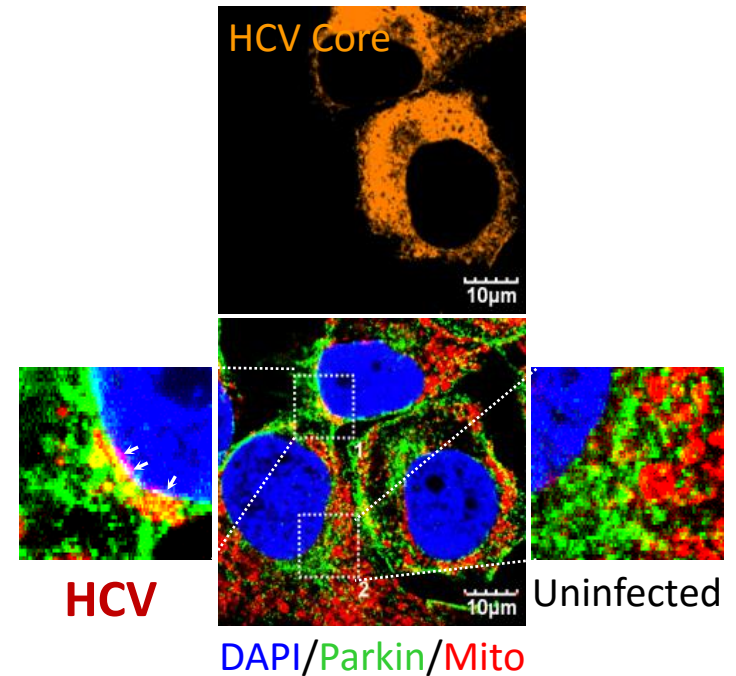
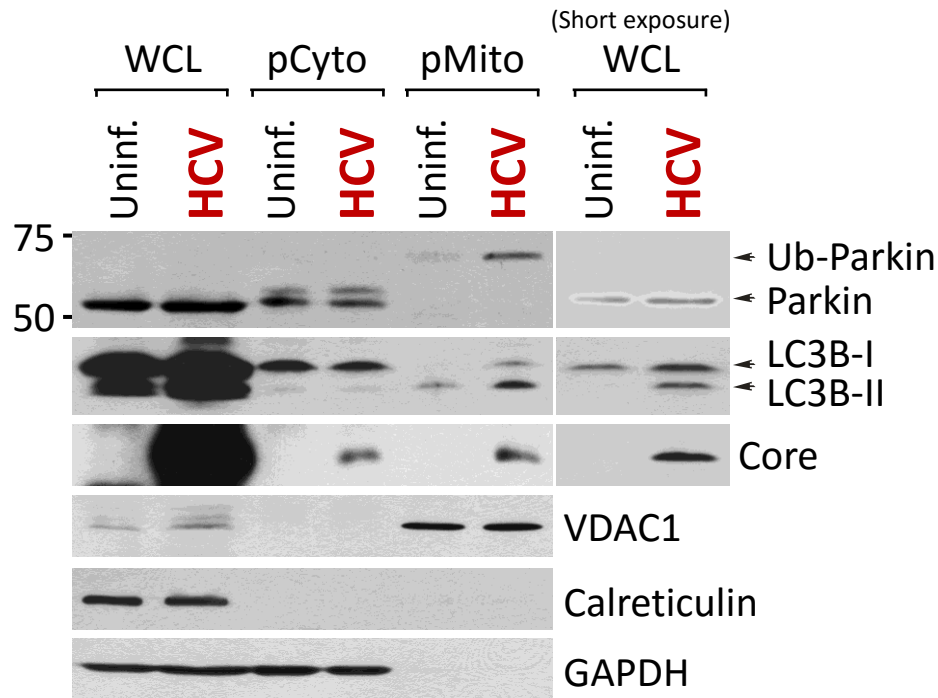
***HBV & HCV***  
***Induce Mitophagy***

# HCV: Stimulates Parkin and PINK1 Expression

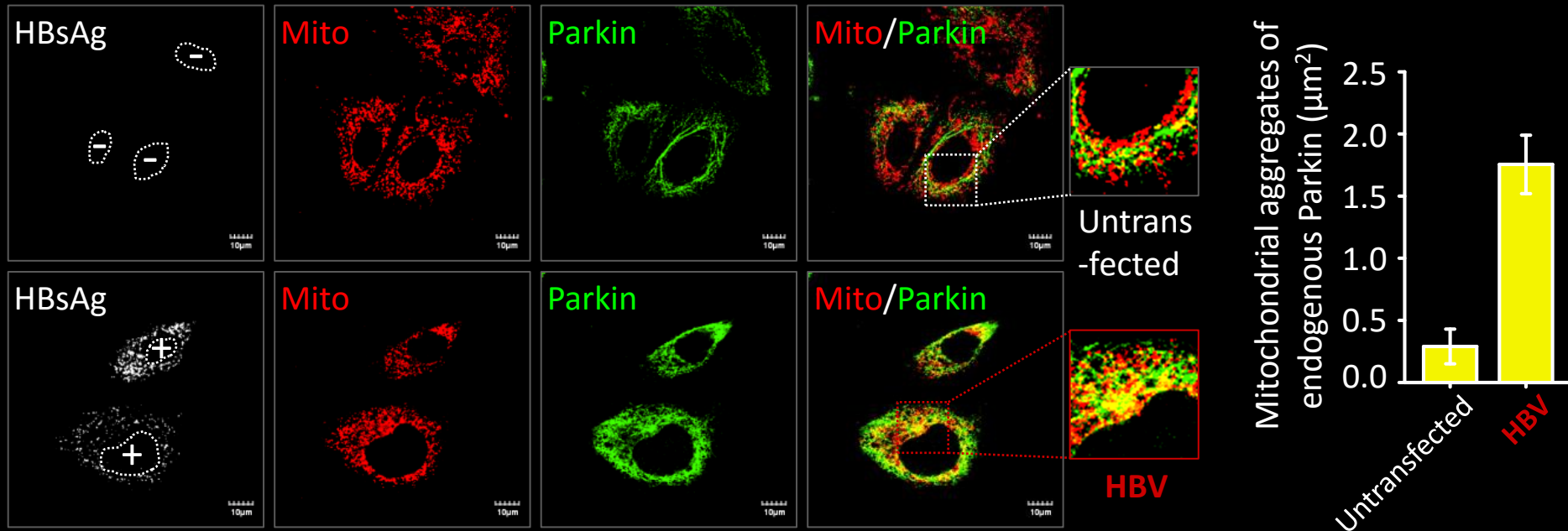


**Note: HBV Also Stimulates Parkin and PINK1 Expression**

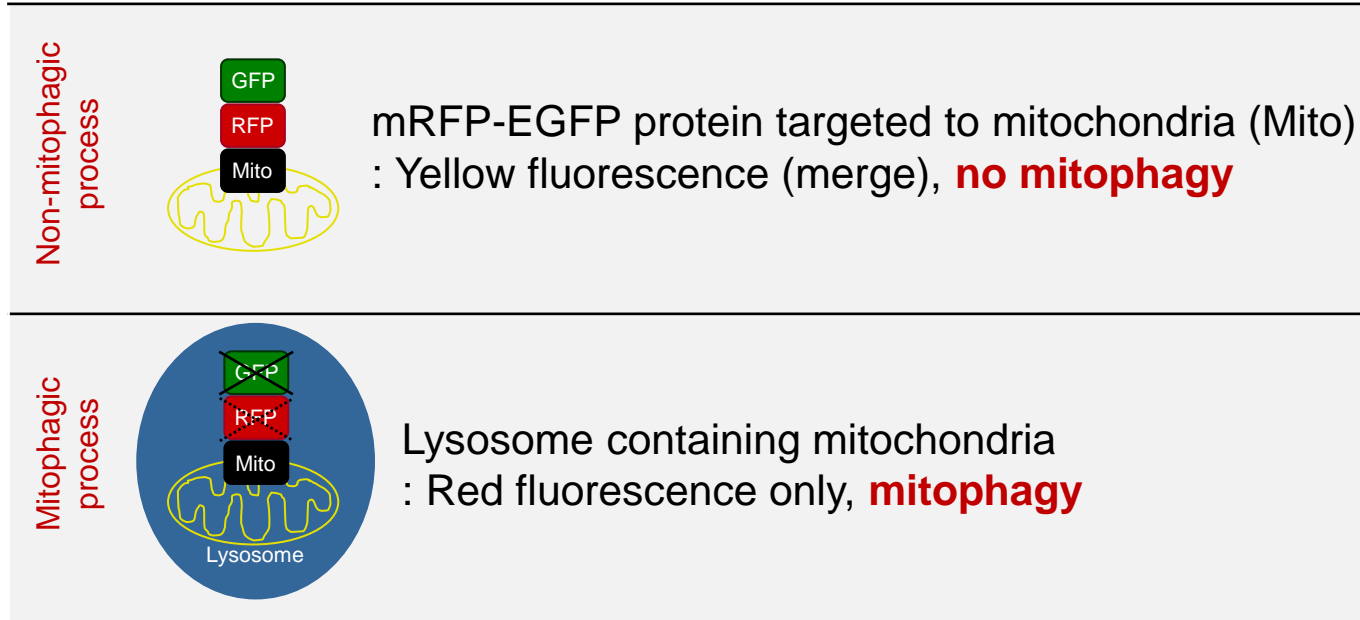
# HCV: *Induces Parkin Translocation to Mitochondria*



# HBV Induces Parkin Translocation to Mitochondria

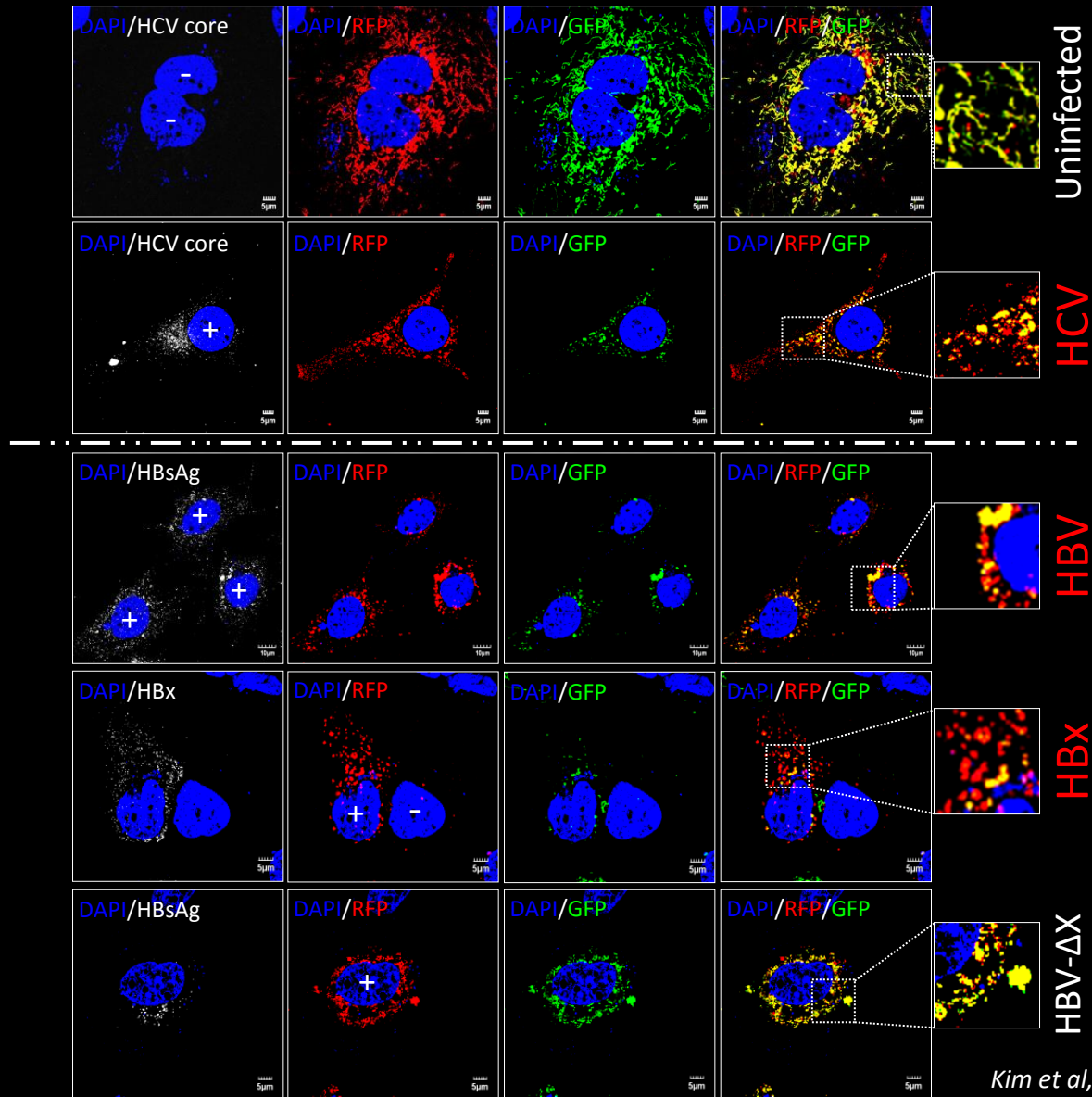


# A novel system for monitoring mitophagy

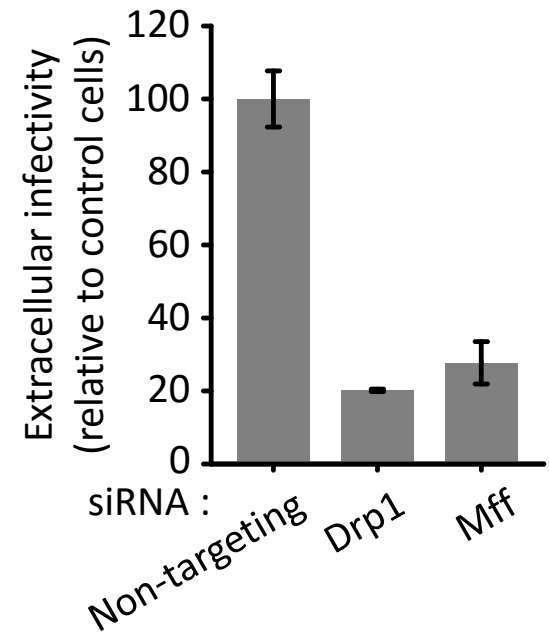
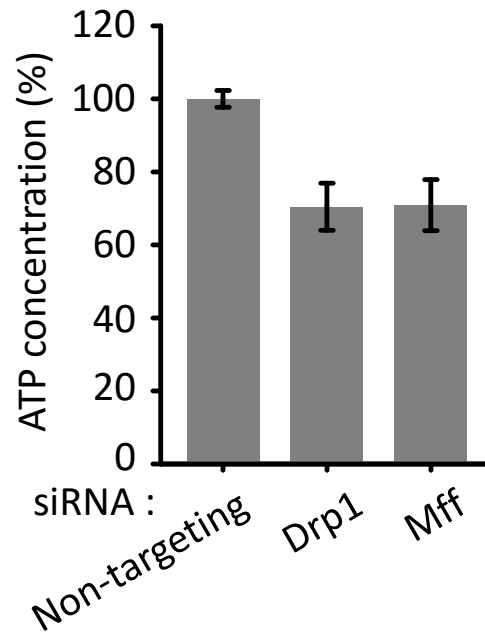
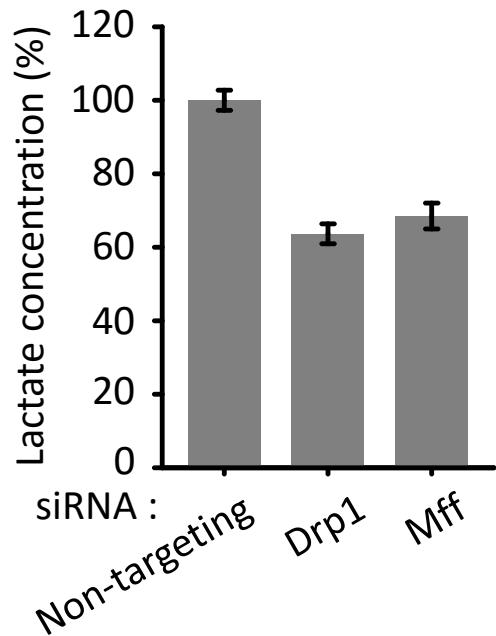




# HBV & HCV: *Induces Complete Mitophagy*

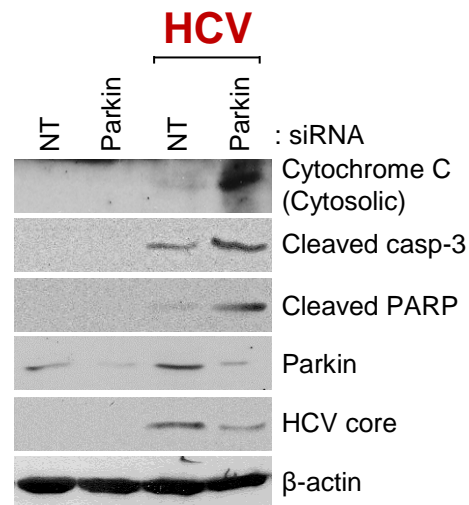
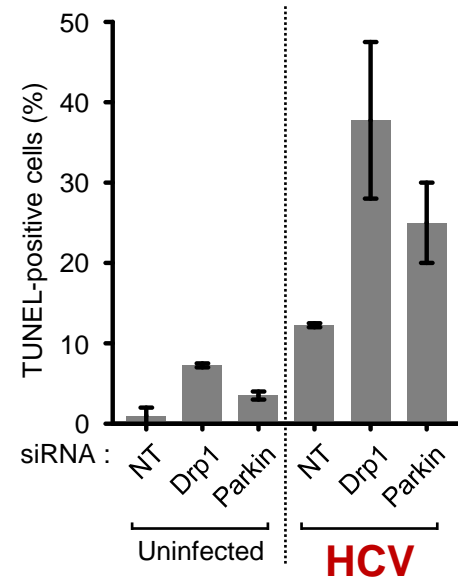
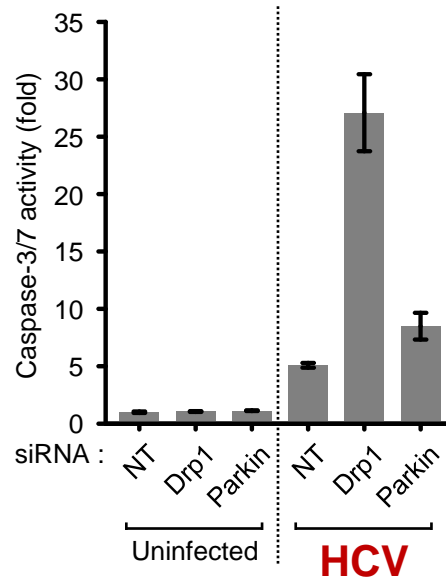
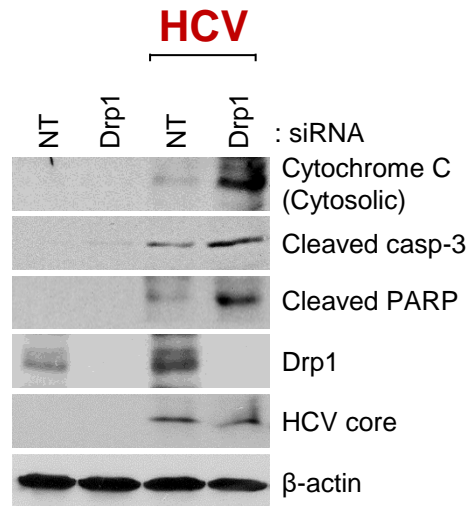


# Mitochondrial fission facilitates HCV secretion



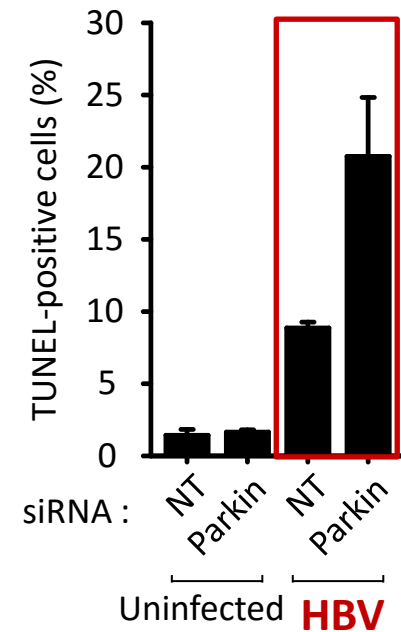
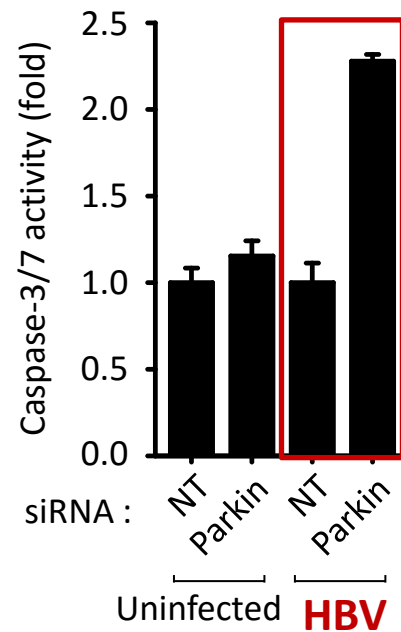
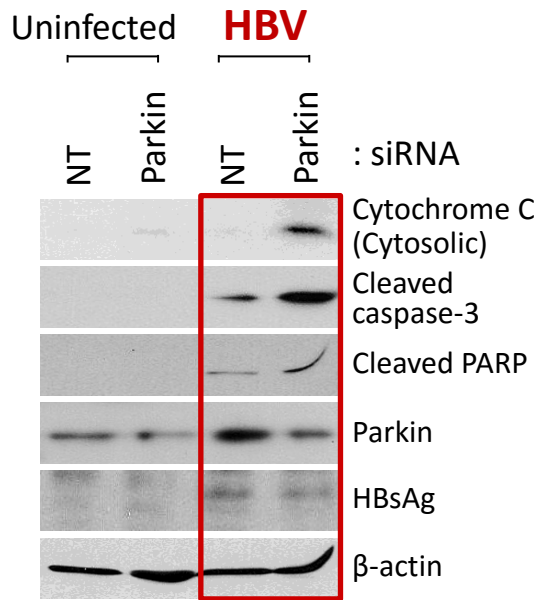
***Effect on mitochondrial dynamics  
on liver diseases***

# HCV: Interference of Mitochondrial Fission and Mitophagy Enhances Apoptotic Cell Death



- Robust cytochrome C release
- Enhancement of caspase-3 activity
- Increase of caspase-3 and PARP cleavage
- Increase of TUNEL-positive cells

# HBV: Interference of Mitophagy Enhances Apoptotic Cell Death



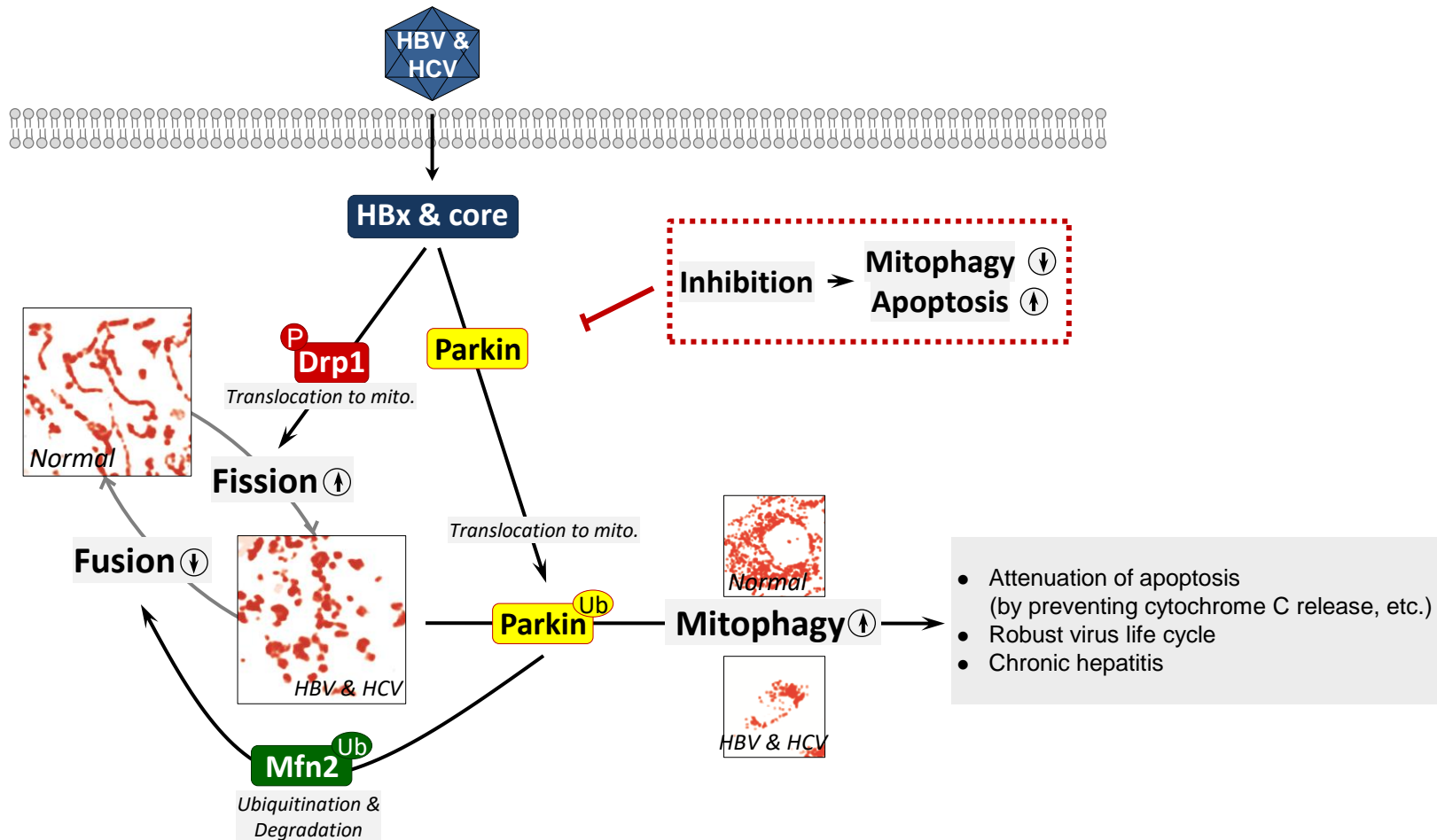
# Summary

Hepatitis B and C viruses (HBV & HCV)

- 1) promote mitochondrial fission
- 2) induce mitophagy

**HBV & HCV modulate mitochondrial dynamics that serve to maintain persistent viral infection and contribute to chronic hepatitis B & C**

# A Model Elucidating HBV & HCV-induced Aberrant Mitochondrial Dynamics in Mitochondrial Apoptosis



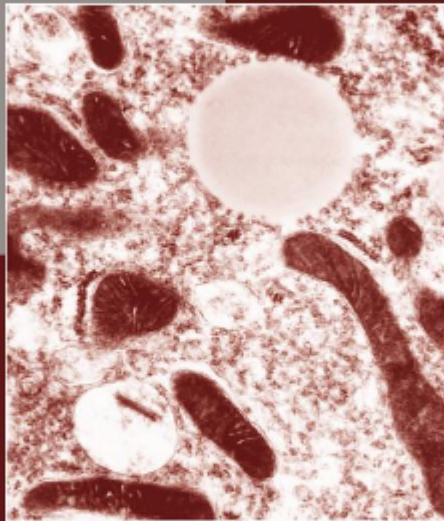
Kim et al, PLoS Pathog, 2013, 12: e1003722

Kim et al, PLoS Pathog, 2013, 3:e1003285

Kim et al, PNAS, 2014, 111:6413-6418

# The Emerging Role of Mitochondrial Dynamics in Viral Hepatitis

## MITOCHONDRIA IN LIVER DISEASE



EDITED BY  
**DERICK HAN**  
**NEIL KAPLOWITZ**

 **CRC Press**  
Taylor & Francis Group

## 14 The Emerging Role of Mitochondrial Dynamics in Viral Hepatitis

*Seong-Jun Kim, Gulam Syed, Sohail Mohammad, Mohsin Khan, and Aleem Siddiqui*

### CONTENTS

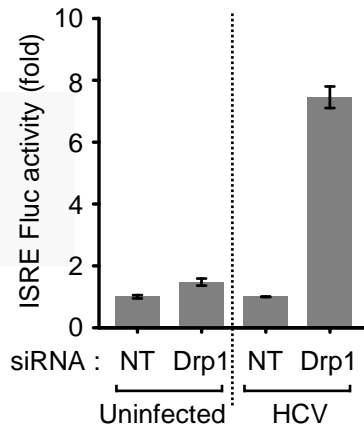
Abstract.....	327
Introduction.....	328
Hepatitis B Virus.....	329
Hepatitis C Virus.....	330
Physiological Perturbation Associated with HBV and HCV Infections.....	331
Mitochondrial Dynamics: Fission, Fusion, and Mitophagy.....	333
HBV and HCV Infections and Mitochondrial Dynamics.....	336
HBV and HCV Infections and Mitophagy.....	337
Mitochondrial Dynamics and Mitophagy: HBV/HCV Viral Persistence.....	338
Mitochondrial Dynamics: Innate Immune Signaling and Inflammasome.....	338
Mitochondrial Dysfunctions: Viral Hepatitis and Nonalcoholic Steatohepatitis (NASH).....	340
Conclusion.....	340
Acknowledgments.....	341
References.....	341

### ABSTRACT

Mitochondrion is a multifunctional organelle, which plays a central role in vital cellular signaling events including cellular homeostasis. Many viruses target mitochondria to facilitate viral proliferation and mitochondrial aberrations incurred during viral infections, which form the basis for the onset of disease pathogenesis. Alterations to the ultrastructure and function of mitochondria are due to a typical phenotype commonly observed in chronic viral hepatitis caused by hepatitis B and C viruses (HBV and HCV). Both HBV and HCV induce endoplasmic reticulum and oxidative stress that perturb cellular calcium homeostasis and trigger mitochondrial damage and injury. Recent studies demonstrate that HBV and HCV disrupt host cell mitochondrial dynamics and upregulate mitochondrial quality control pathways to eliminate mitochondria damaged during the course of infection. Both HBV and HCV induce mitochondrial fission by triggering the mitochondrial recruitment of fission protein dynamin-related protein 1 (Drp1), which allows the segregation of



# Does virus-induced aberrant mitochondrial dynamics affect innate antiviral immunity?



*Investigating mitochondrial fission and mitophagy's key factors in innate immune response*

(Kim et al, PNAS, 2014, 111:6413-6418)