A gut microbiota-bile acid axis inhibits the infection of an emerging coronavirus by targeting its cellular receptor aminopeptidase N

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Introduction

The Discovery History of *Deltacoronavirus*

2006

Hong Kong-based scholars Dong et al. detected novel coronaviruses in fecal samples from wild Asian leopard cats (*Prionailurus bengalensis*) and Chinese ferret badgers (*Melogale moschata*)

2009

Woo et al. from Hong Kong first reported the identification of three novel coronaviruses of avian origin in wild bird communities:

- HKU11
- HKU12
- HKU13

2012

Woo et al. identified seven deltacoronavirus strains in pigs and wild birds:

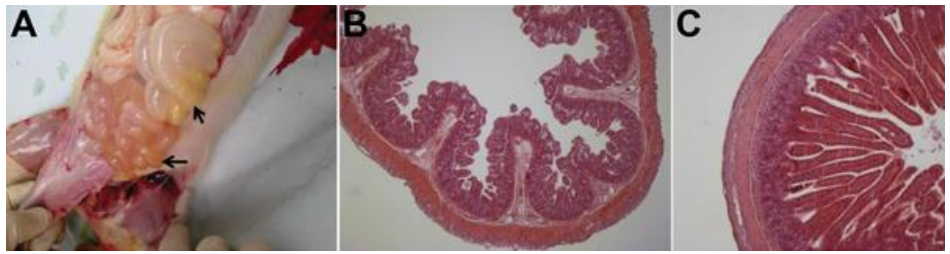
- HKU15;
- HKU16, HKU17, HKU18, HKU19, HKU20, HKU21;

2014

PDCoV was initially identified during a diarrheal disease outbreak in piglets in Ohio, USA, marking its first isolation.

Subsequently, PDCoV has been detected in South Korea, India, Thailand, and mainland China.

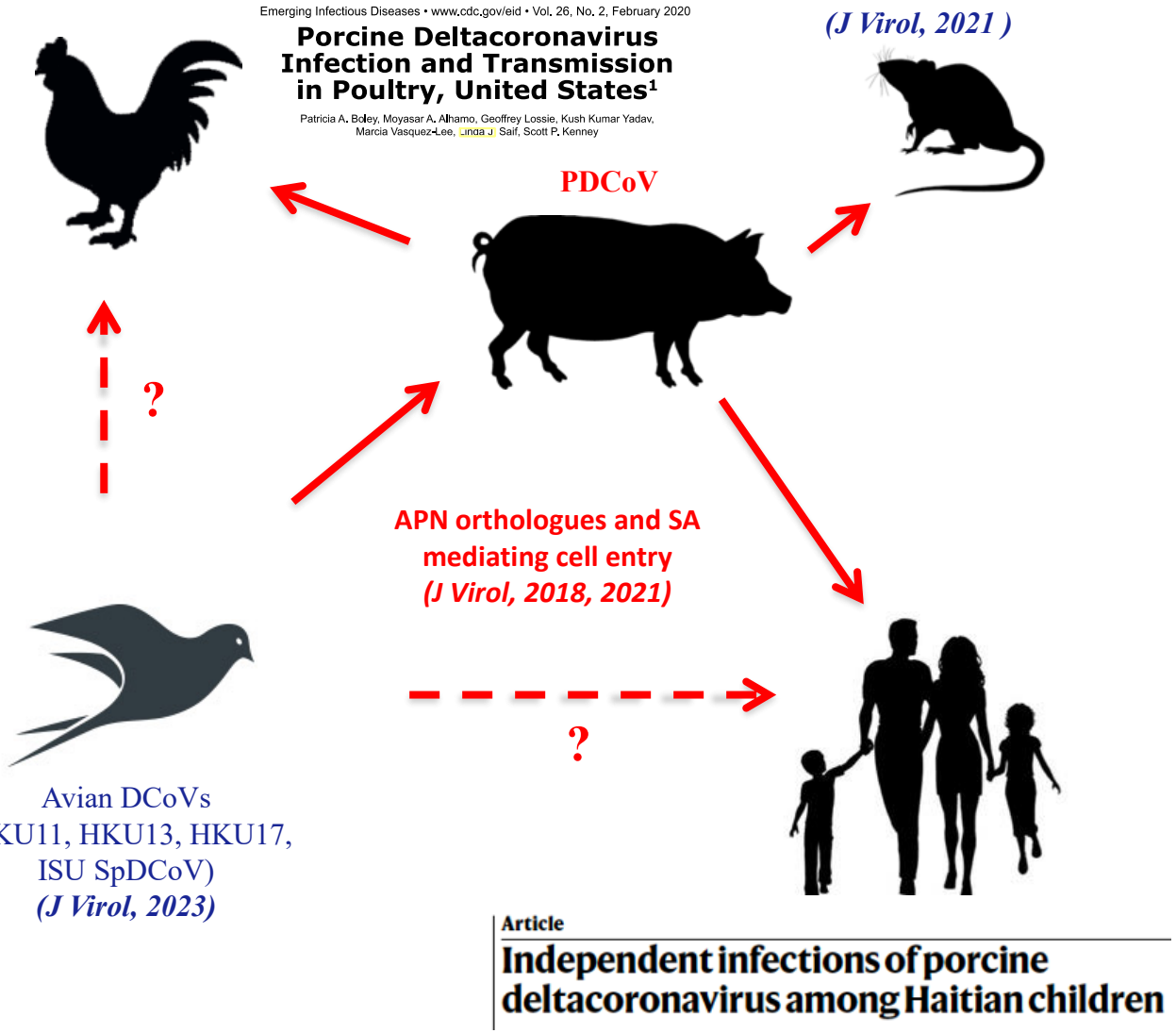
(Patrick C. Y. Woo et al., 2012)



(Kwonil Jung, et al. 2015)

Introduction

◆ The Molecular Basis of PDCoV Cross-Species Transmission— Aminopeptidase N



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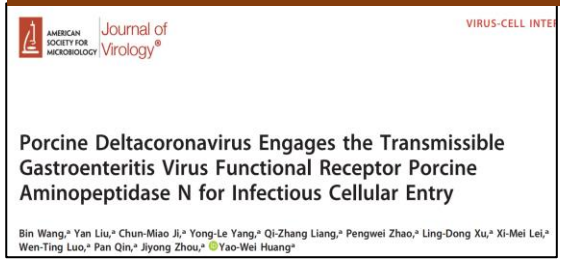
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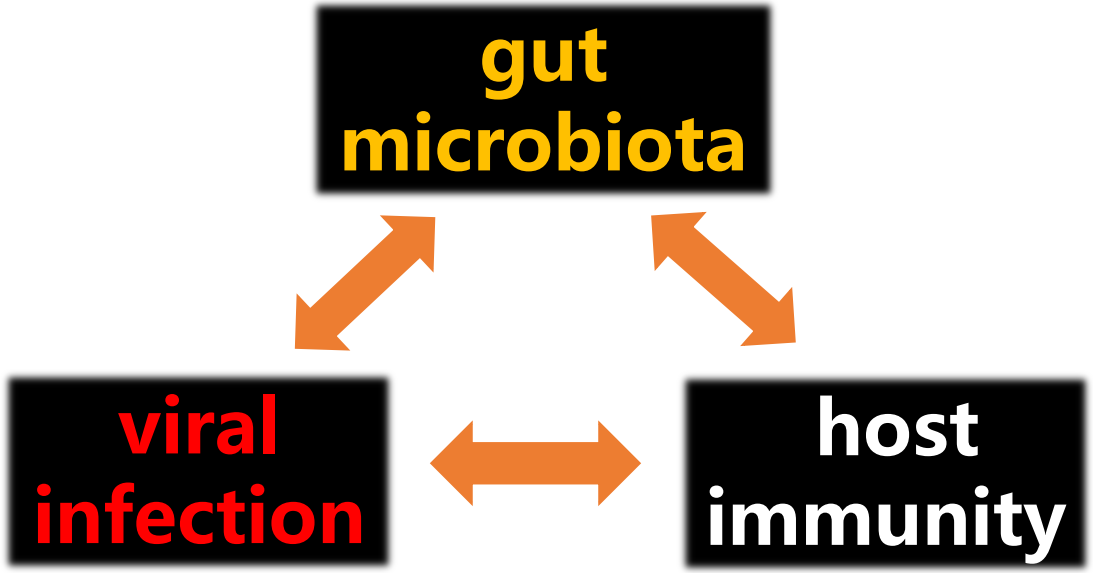
Chicken or Porcine Aminopeptidase N Mediates Cellular Entry of Pseudoviruses Carrying Spike Glycoprotein from the Avian Deltacoronaviruses HKU11, HKU13, and HKU17

- ❖ Our group was the first to identify porcine aminopeptidase N (APN) as the functional cellular entry receptor for PDCoV
- ❖ We further demonstrate that PDCoV utilizes human, chicken, feline, or murine APN for cellular entry, with sialic acid (SA) serving as a co-receptor.
- ❖ Pseudotyped viruses of three wild avian deltacoronaviruses exhibit cellular entry via either chicken APN or porcine APN.

Scientific question



Limitations of existing studies:

- A narrow focus solely on virus-host interactions.
- Limited incorporation of the realistic gut microenvironment, leading to inadequate mechanistic exploration.

Research Objectives

(1) To identify the gut microbiota and metabolites most strongly associated with host immune regulation during PDCoV infection and to elucidate their key immune targets.

(2) To investigate the molecular mechanisms by which these metabolites modulate PDCoV infection.

Result

◆ PDCoV infection significantly alters the composition of the gut microbiota

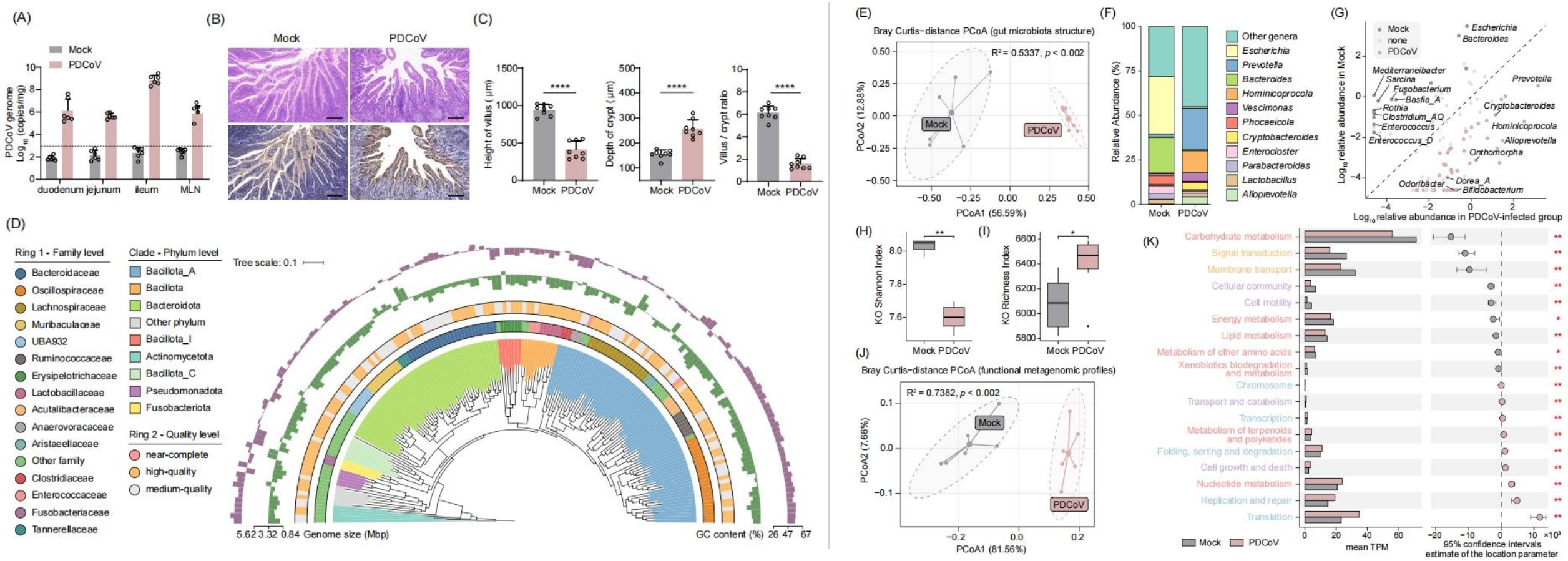


Figure 1. Effect of PDCoV infection on the balance of intestinal microbiota.

Result

◆ Gut commensal *Bacteroides fragilis* was closely associated with PDCoV replication

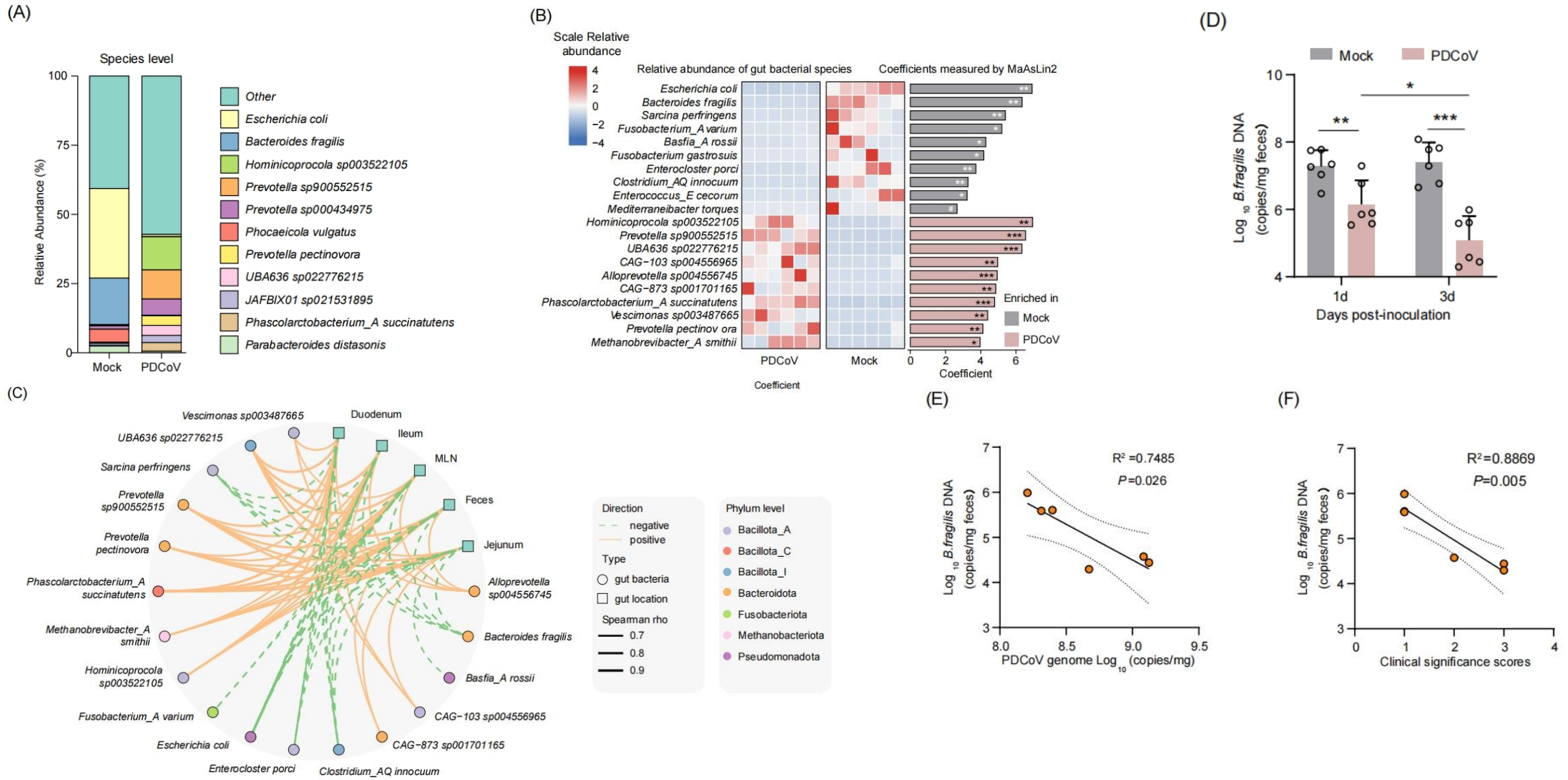


Figure 2. PDCoV replication is associated with depletion of *Bacteroides fragilis*.

Result

◆ PDCoV-induced *B. fragilis* depletion drives conjugated bile acid accumulation

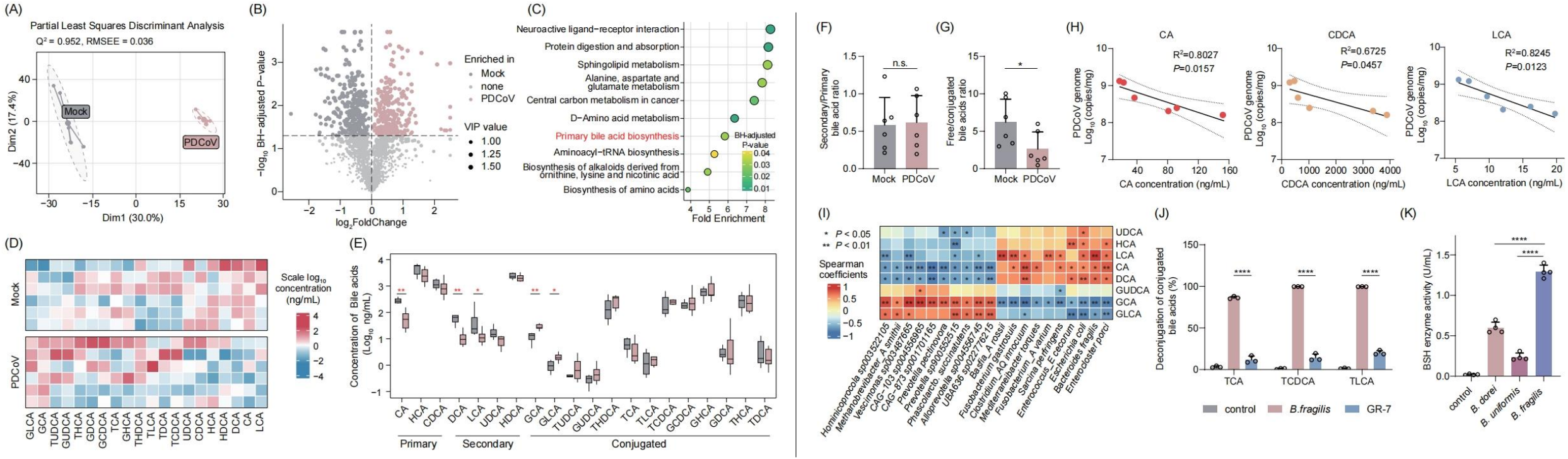


Figure 3. Significant changes in intestinal bile acids of piglets following oral PDCoV infection.

Result

◆ *B. fragilis*-mediated elevation of unconjugated bile acids significantly inhibited PDCoV infection in mice

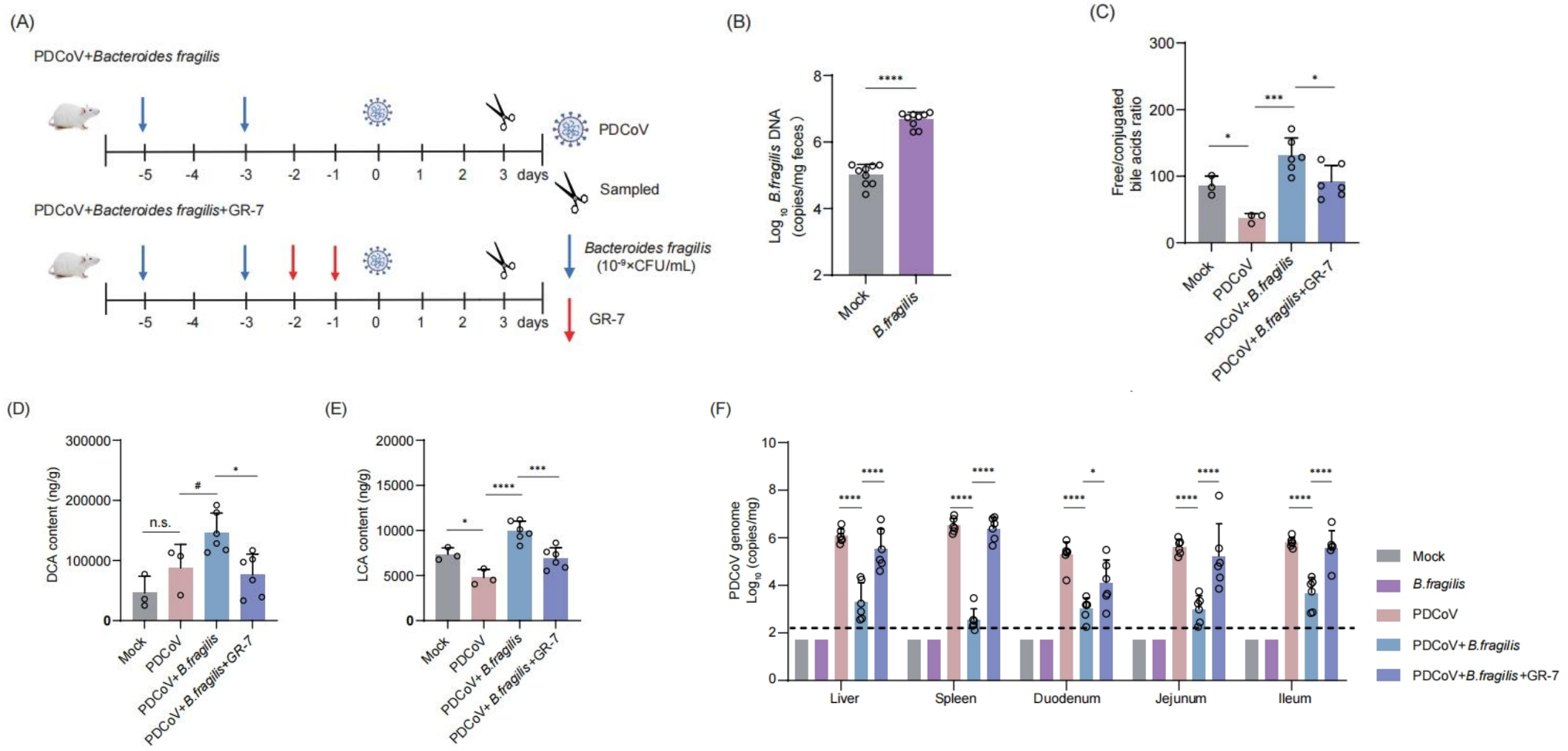


Figure 4. Impact of BSH-producing *B. fragilis* colonization on bile acid composition and PDCoV dynamics.

Result

◆ LCA effectively inhibits PDCoV infection in IPEC-J2 cells and porcine intestinal enteroids

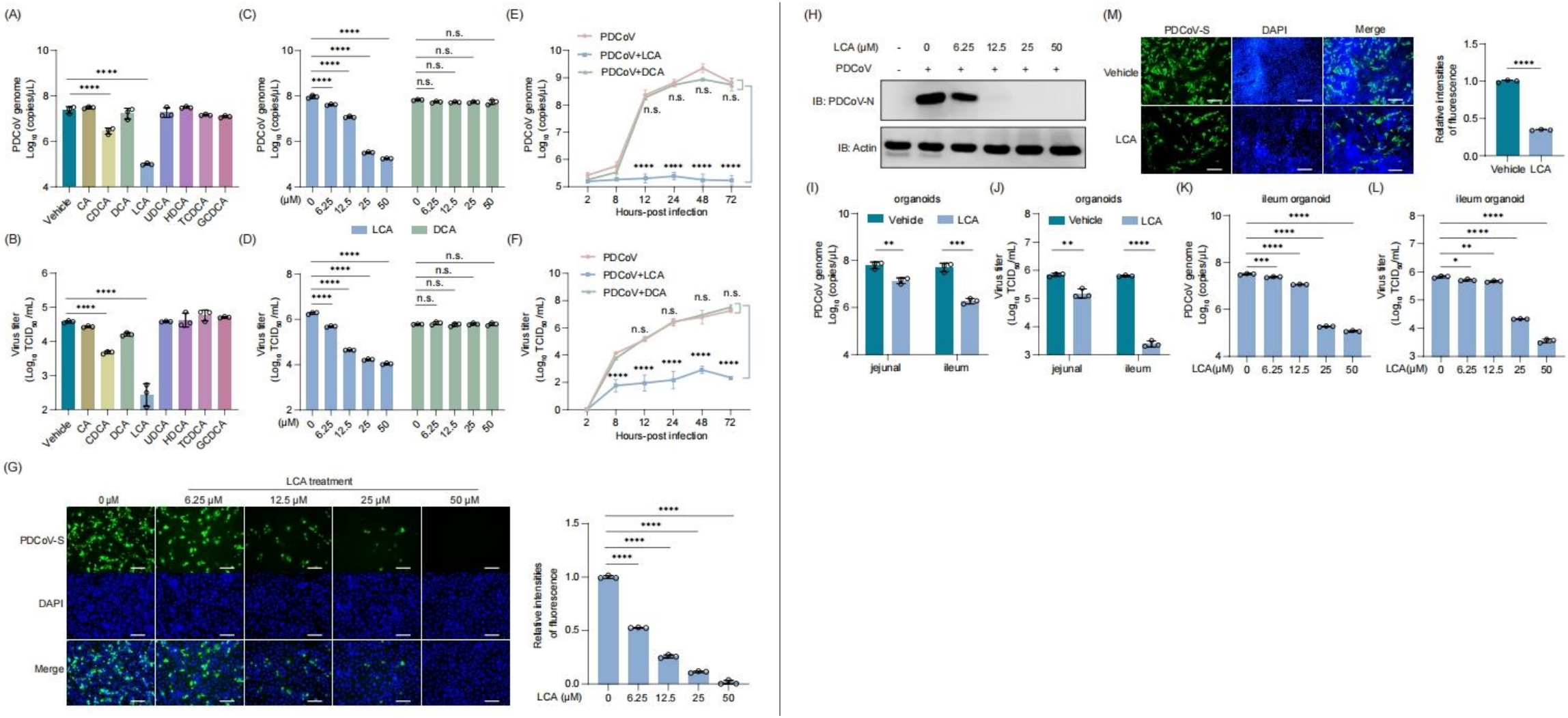


Figure 5. LCA inhibits PDCoV infection in porcine small intestinal epithelial cells and porcine intestinal enteroids.

Result

◆ LCA inhibits the binding of PDCoV spike proteins to pAPN

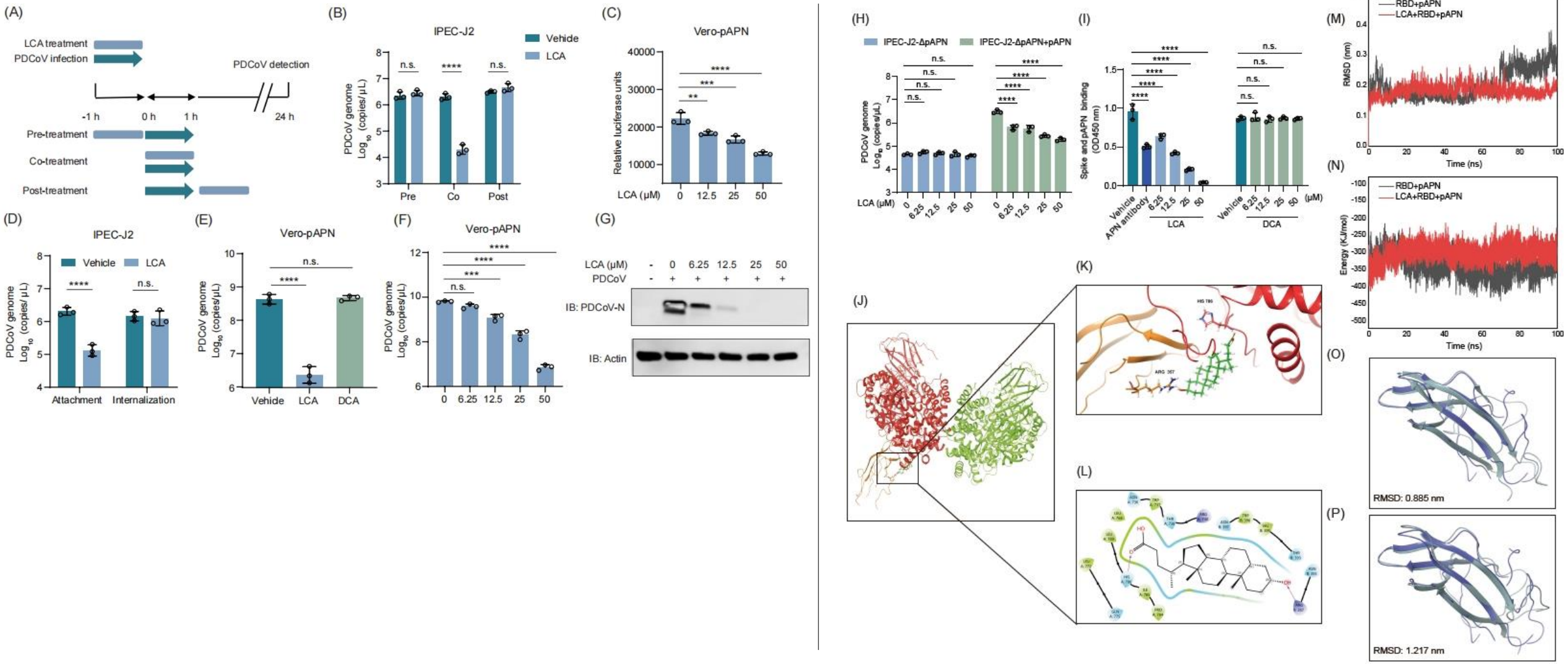


Figure 6. LCA inhibits PDCoV infection by disrupting viral entry by blocking spike-pAPN interaction and inducing conformational changes in the RBD-pAPN complex.

Result

◆ LCA effectively inhibits PDCoV infection in piglets

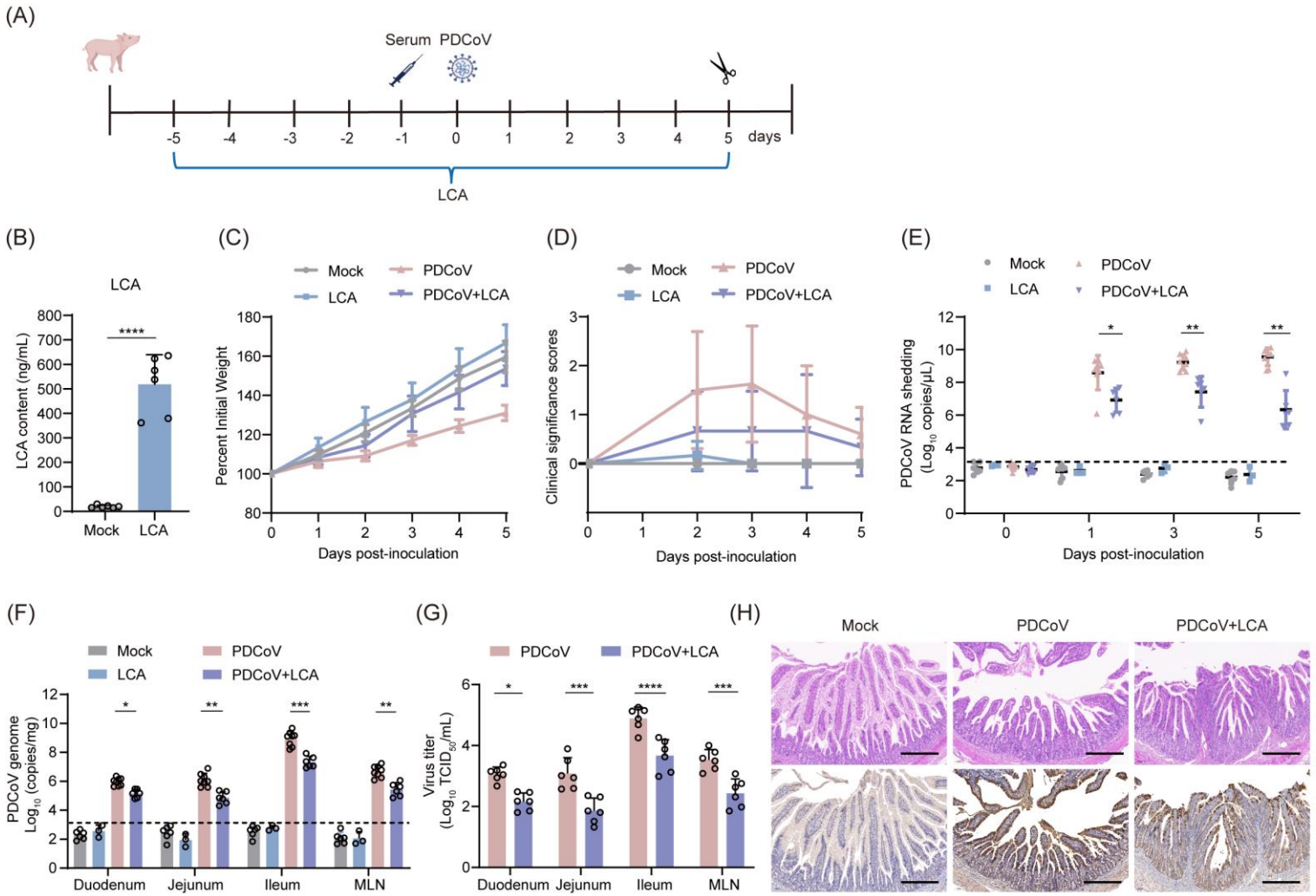
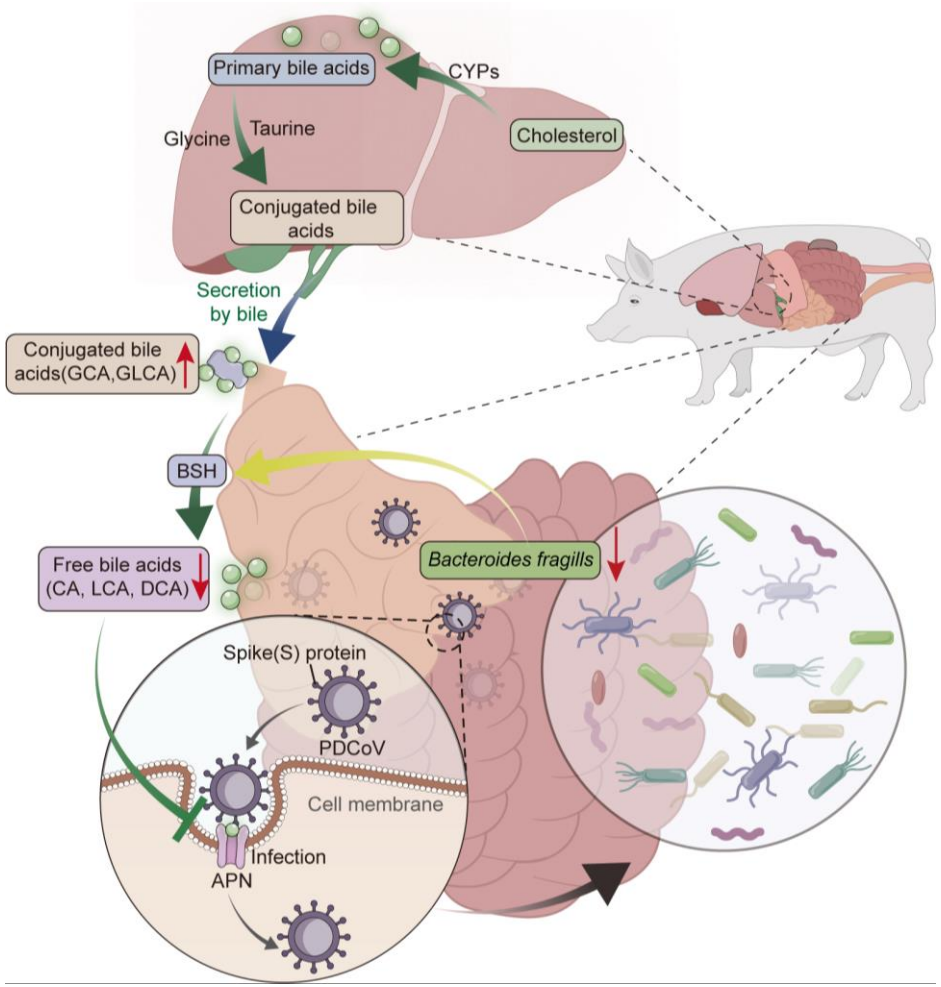


Figure 7. The effect of LCA on PDCoV infection in piglets.

Summary



- Through integrated multi-omics analysis, we have for the first time characterized PDCoV-triggered dysregulation of the gut microbiota-bile acid axis and delineated its pathological consequences.
- We demonstrate that *B. fragilis* exerts antiviral effects against PDCoV through BSH-dependent regulation of bile acid metabolism, establishing a microbiota-derived protective mechanism against enteric coronaviruses.
- We for the first time reveal a novel molecular mechanism by which LCA inhibits PDCoV invasion through directly blocking the interaction between the viral spike protein and host receptor aminopeptidase N.

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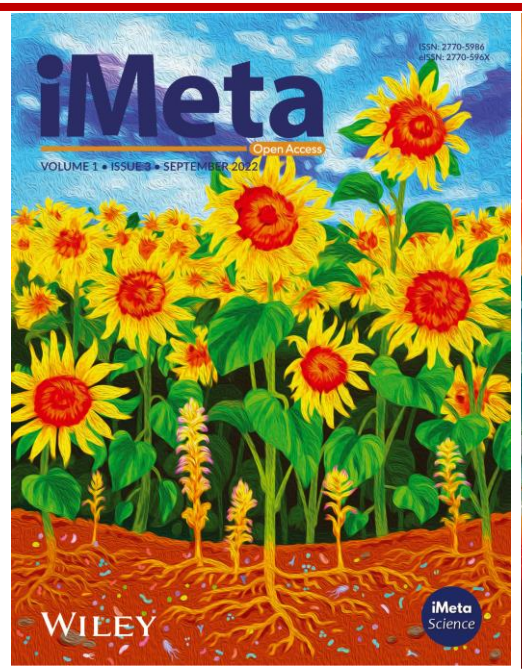

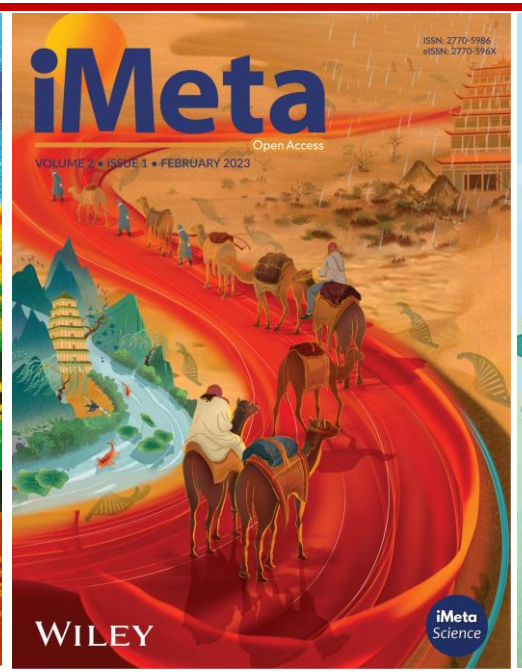

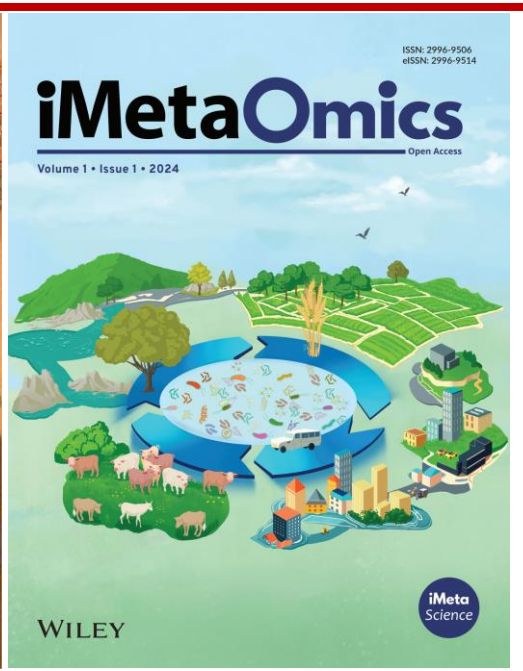

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