Curcuminoids Amplify Host Innate Antiviral Immunity via the CRYAB-RBM26 Axis in Viral Infection

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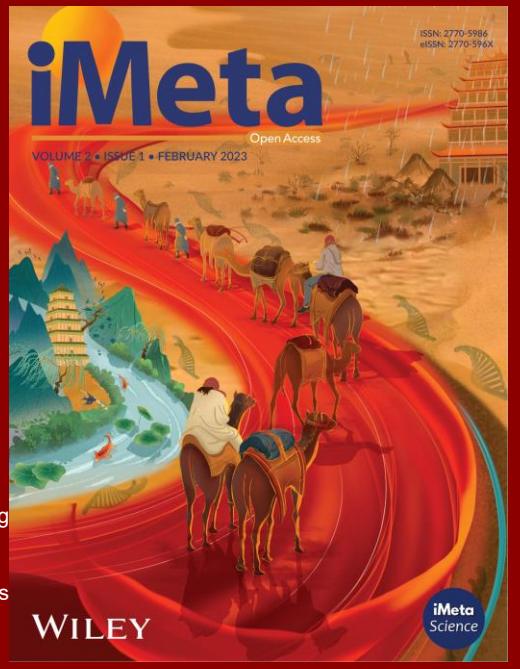

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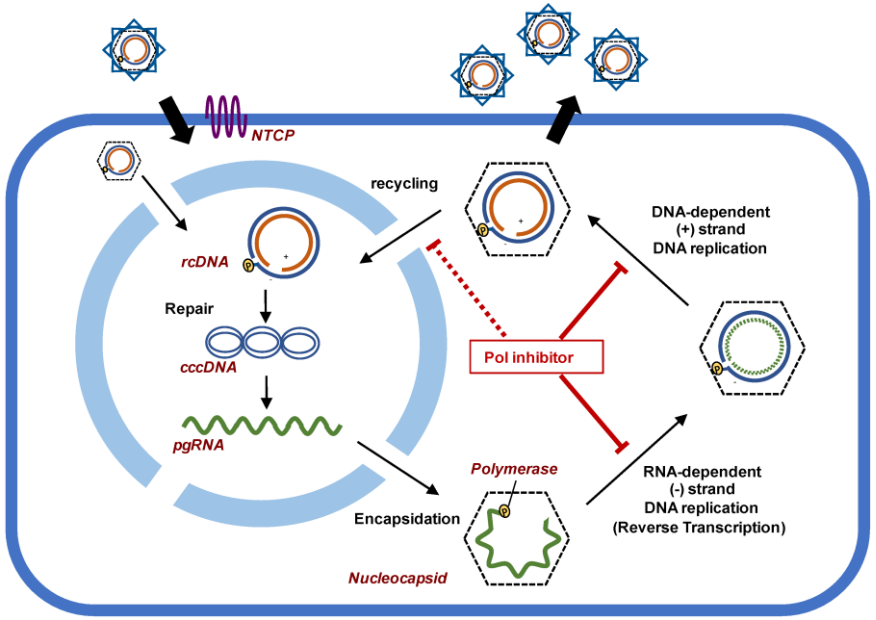
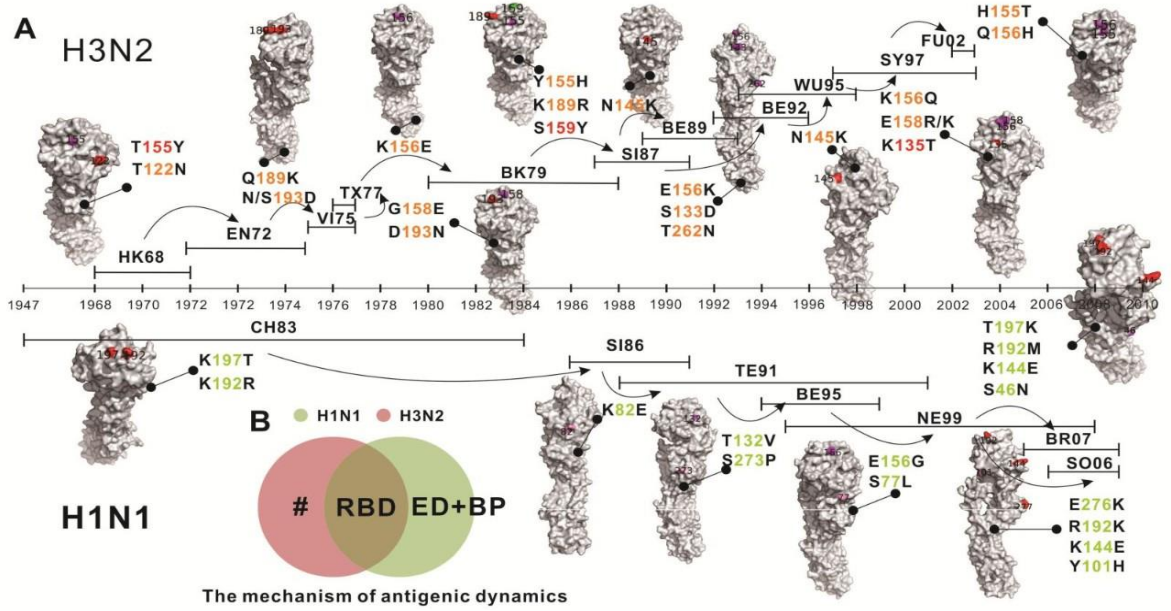
Introduction



Target-drug

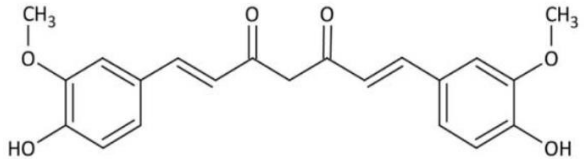
Vaccines



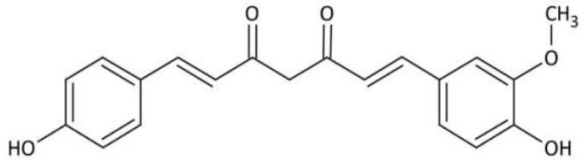
Emergence of viral variants

Traditional antiviral durg develpment faces challengs like drug resistance, toxicity, and limited scope. Therefore, exploreing natural products as potential antivirals is a key research focus.

Introduction



curcumin(CUR)



Demethoxycurcumin(DMC)

CUR is widely used, and DMC exhibits better solubility.

Is IFN-I activation the common key mechanism for the antiviral effects of both curcuminoids?

What is the complete molecular pathway linking curcuminoids to IFN-I regulation??

Curcumin modulation of **IFN**-beta and IL-12 signalling and cytokine induction in human T cells.

Fahey AJ, Adrian Robins R, Constantinescu CS.

J Cell Mol Med. 2007 Sep-Oct;11(5):1129-37. doi: 10.1111/j.1582-4934.2007.00089.x.

PMID: 17979888 Free PMC article.

IFN-beta-induced STAT4 phosphorylation, IL-10 production and **IFN** receptor (IFNAR) subunits 1 and 2 expression were enhanced by **curcumin**. **Curcumin** increased **IFN**-alpha-induced IL-10 and IFNAR1 expression. Prior exposure to **curcumin** decrease

Curcumin activates the JAK-STAT signaling pathway to enhance the innate immune response against porcine epidemic diarrhea virus infection in vivo and in vitro.

Jiang Q, Liu X, Yuan J, Zhang S, Zhang Y, Kan Z, Niu Z, Zhang L, Hu X, Zhou Y, Wang J, Li F, Cao L, Zhang X, Lei C, Song Z.

Vet Microbiol. 2025 Jun;305:110535. doi: 10.1016/j.vetmic.2025.110535. Epub 2025 Apr 25.

PMID: 40286548

For PEDV, a highly pathogenic virus, cellular autoimmune response is not sufficient to fight against its infection. Our results demonstrated that **curcumin** could exert antiviral effects by enhancing the JAK-

Desmethoxycurcumin aids IFNα's anti-HBV activity by antagonising CRYAB reduction and stabilising IFNAR1 protein

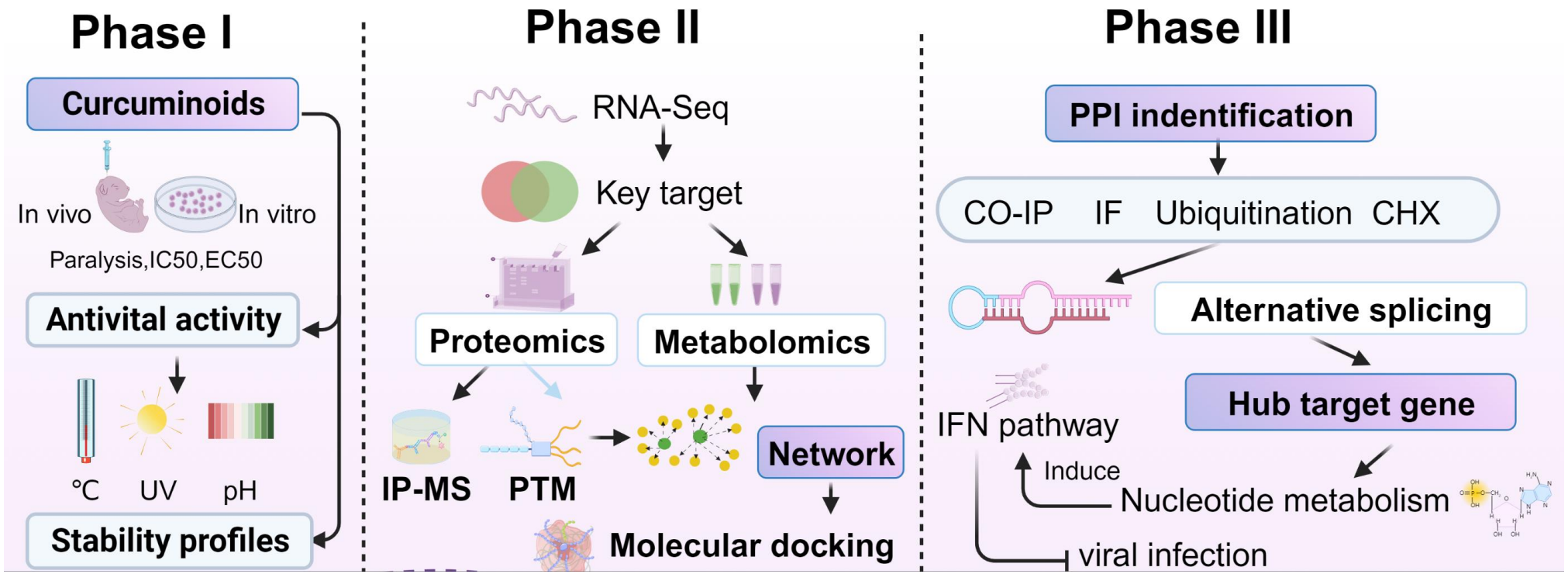
Jinlai Wei [1], Xichuan Deng [2], Wenying Dai [2], Lingxin Xie [2], Guangyuan Zhang [2 3], Xinyue Fan [2], Xinyue Li [2], Zhixing Jin [2], Qin Xiao [4], Tingting Chen [2 3]

Affiliations + expand

PMID: 37851377 DOI: 10.1080/1061186X.2023.2273200

This study aims to elucidate the common molecular mechanism of DMC and CUR against EV-D68, providing new insights for host-directed antiviral strategies.

Research design



Individual differences:

·Physicochemical properties

·Antiviral activity

Common mechanism:

·Use multi-omics to uncover common mechanism and construct a "Drug-downstream target-metabolism network map

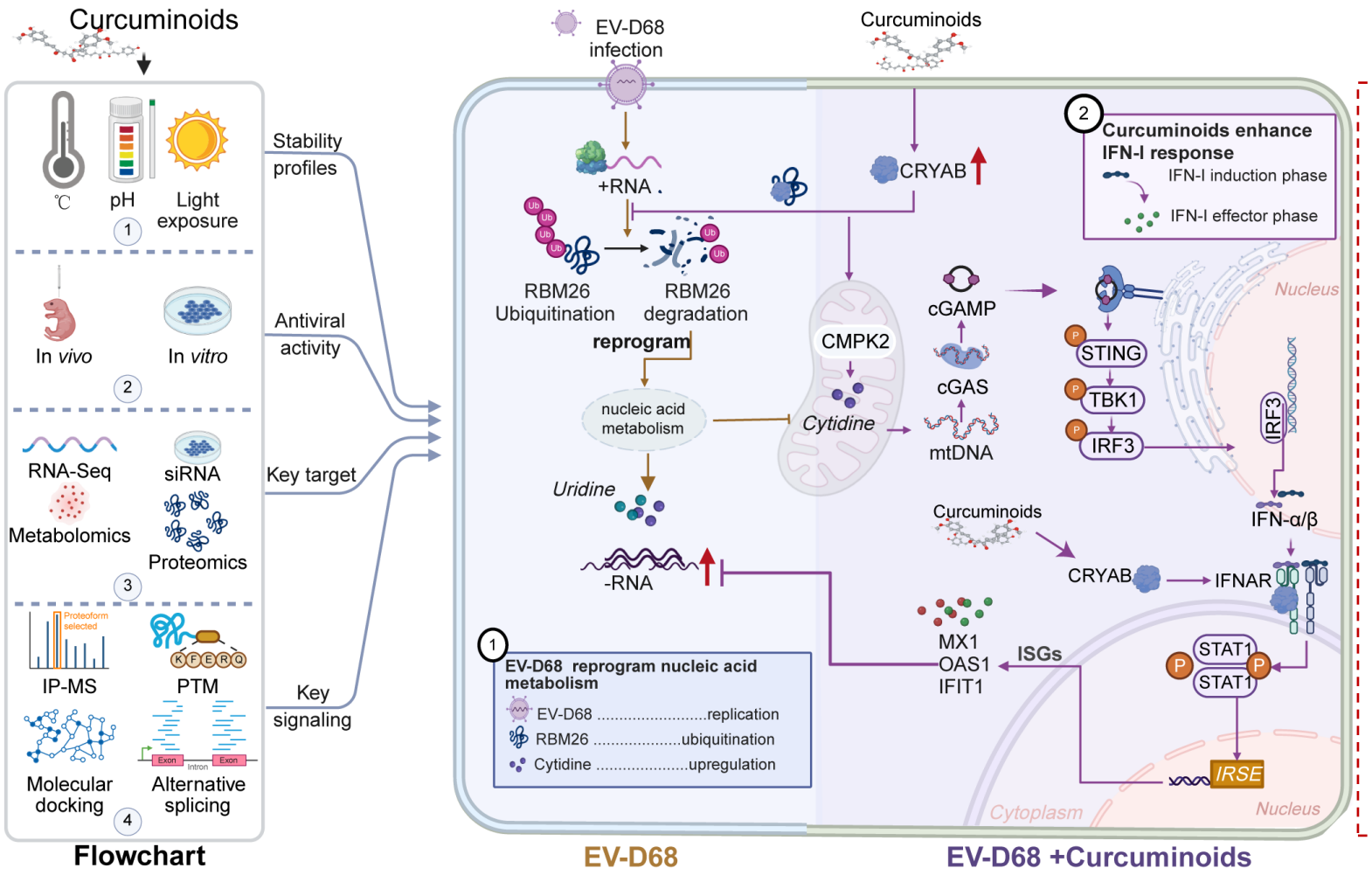
Antiviral molecular chain:

·Elucidate the shared regulatory mechanism from upstream gene transcription to downstream metobolic effectors.

·Establish the link between"Drug-target" and innate immunity.

This approach clarifies the common mechanism of DMC and CUR against EV-D68, broadening the perspective for host-target antiviral strategies.

Highlights



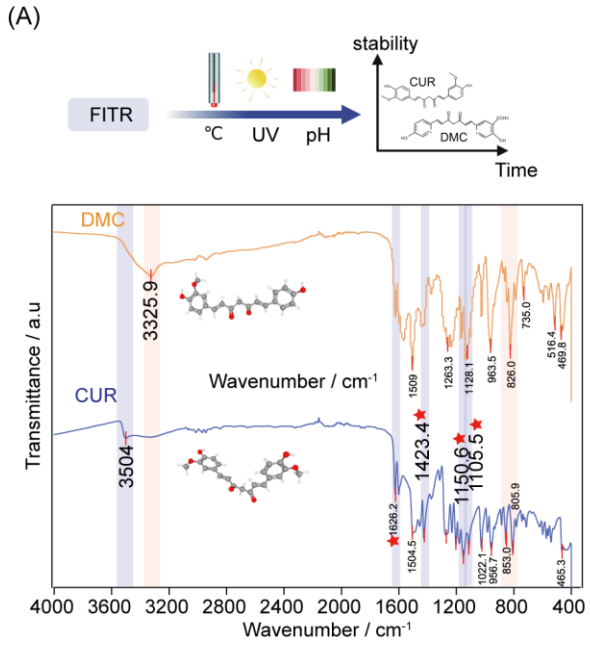
◎CRYAB-RBM26 is identified as a core antiviral regulatory axis of curcuminoids

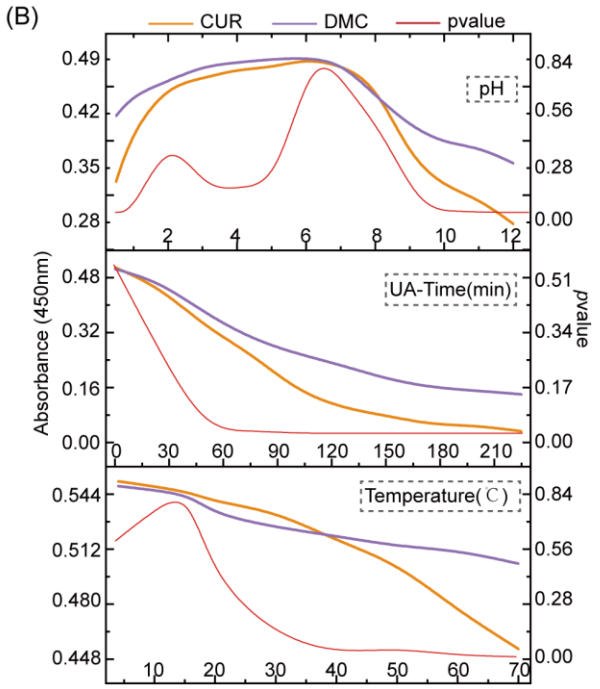
◎Curcuminoids modulate type I interferon signalling in a dual-phase manner

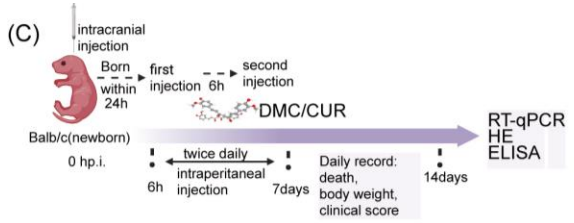
◎Curcuminoids prevent virus-induced hijacking of host nucleotide metabolism in an RBM26-dependent manner

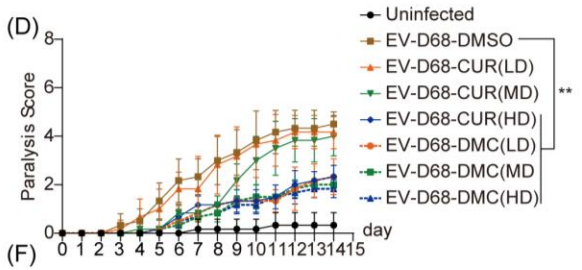
◎Multiomics reveals a compound-target-metabolism-immune cascade that mediates antiviral effects

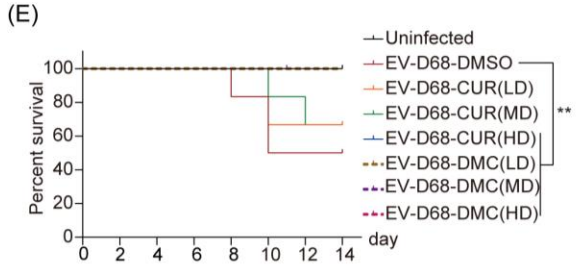
Key results overview-1

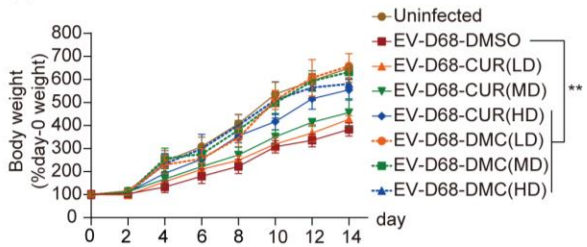


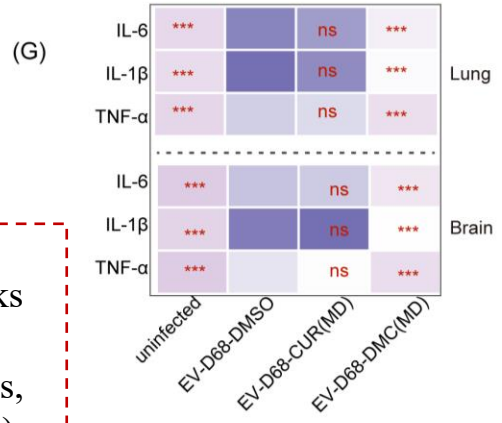


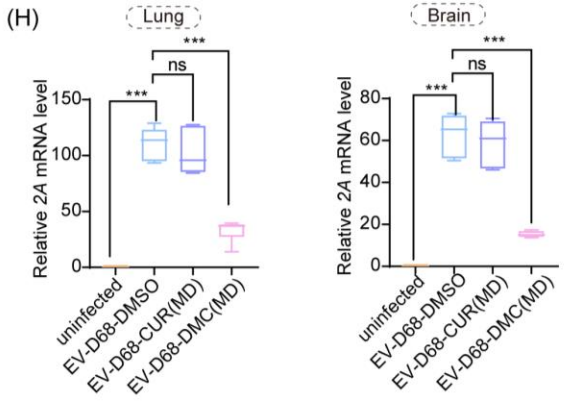












Key results:

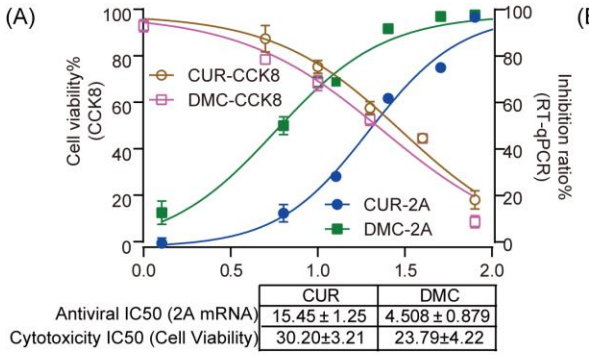
①infrared spectroscopy: DMC showed distince characteristic absorptio peaks compared to CUR.

②Stability Tests: DMC exhibited greater stability under various temperatures, light, and pH conditions, especially in strong acid (pH<3), strong alkali (pH>8), and high temperatures.

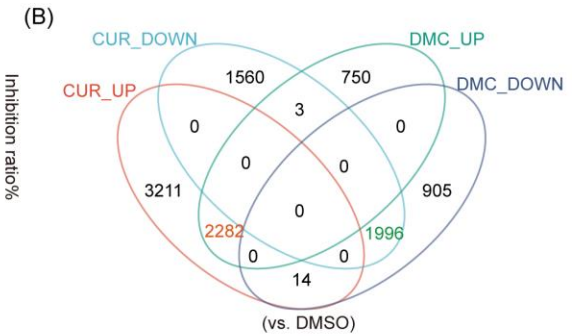
③In Vivo Model: The effective antiviral concentration of DMC was lower than that of CUR.

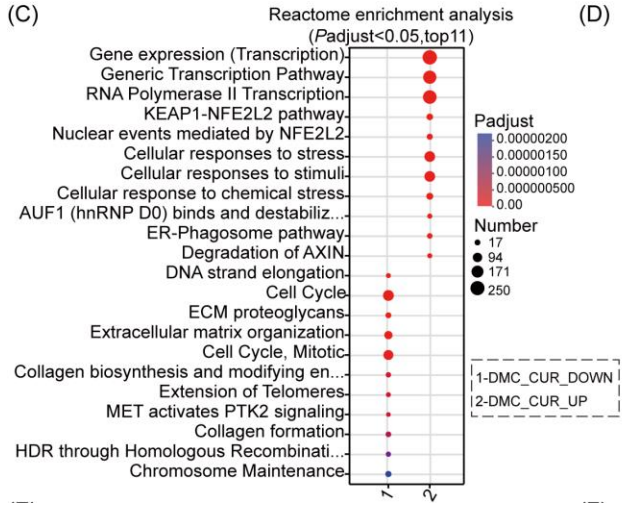
Conclusion:DMC is superior to CUR in both stability and antiviral efficacy.

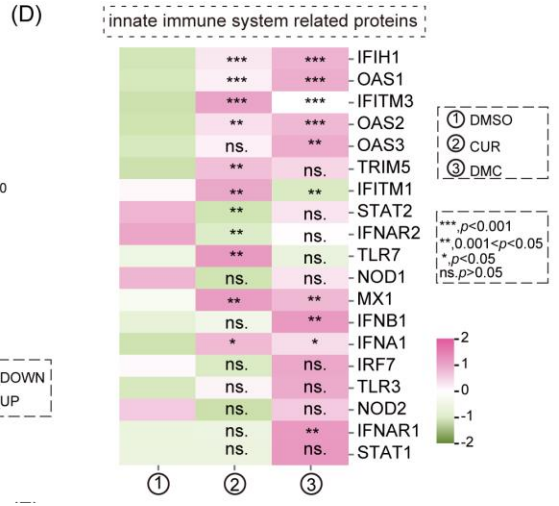
Key results overview-2

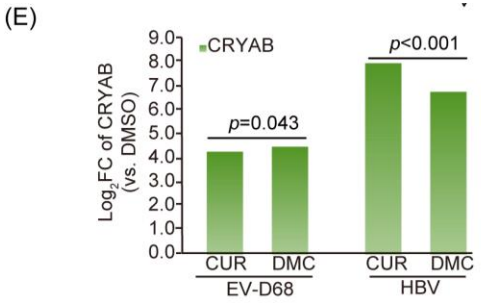


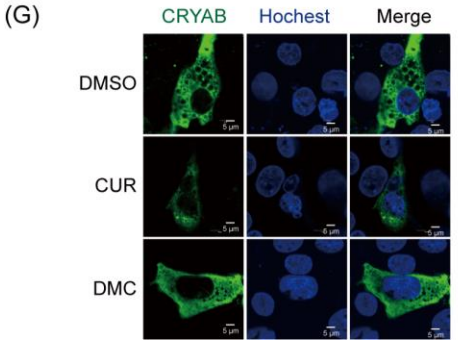
	CUR	DMC
Antiviral IC50 (2A mRNA)	15.45 ± 1.25	4.508 ± 0.879
Cytotoxicity IC50 (Cell Viability)	30.20±3.21	23.79±4.22

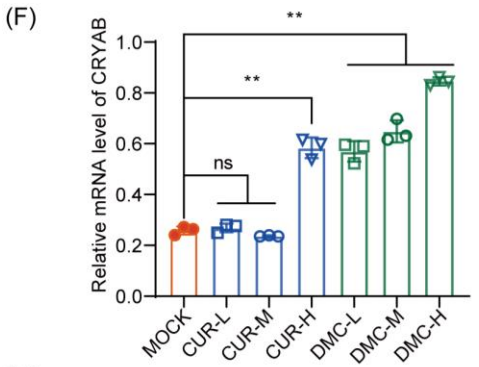


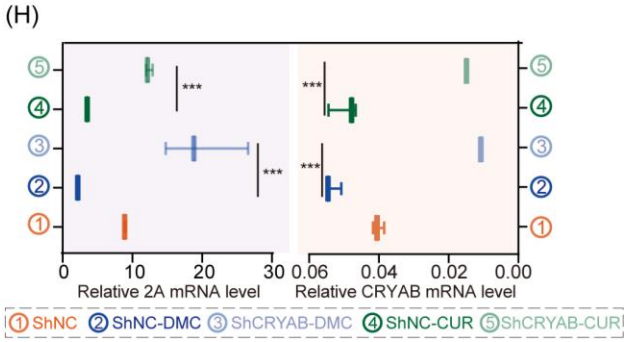












Key results:

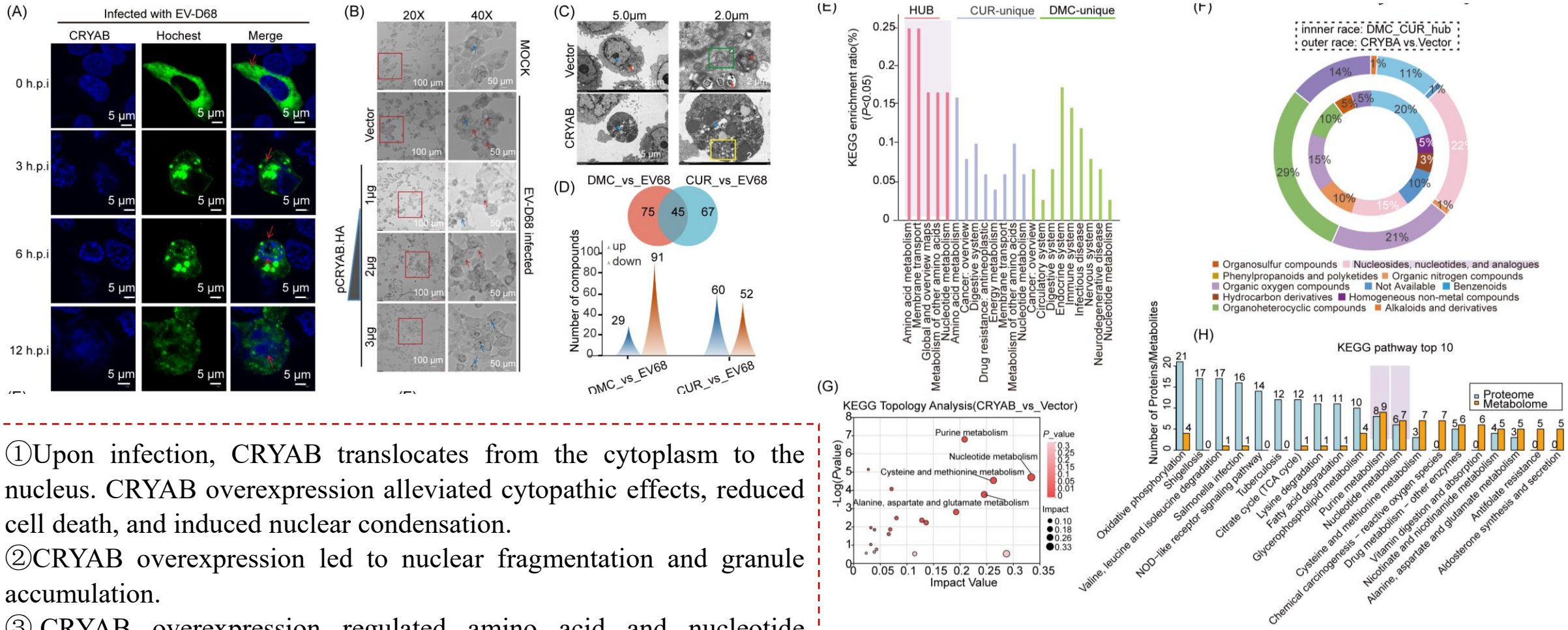
①DMC showed slightly higher cytotoxicity than CUR but exhibited stronger inhibition of the viral 2A gene.

②RNA-seq demonstrated both compounds upregulated immune-related genes (e.g., IFIH1, OAS1, IFITM3).

③Both compounds significantly upregulated CRYAB expression. Knockdown of CRYAB abolished the significant inhibition of viral 2A gene expression by the drugs.

Conclusion: Activation of the innate immune pathway is the common mechanism of curcuminoids, and CRYAB is their common downstream target.

Key results overview-3



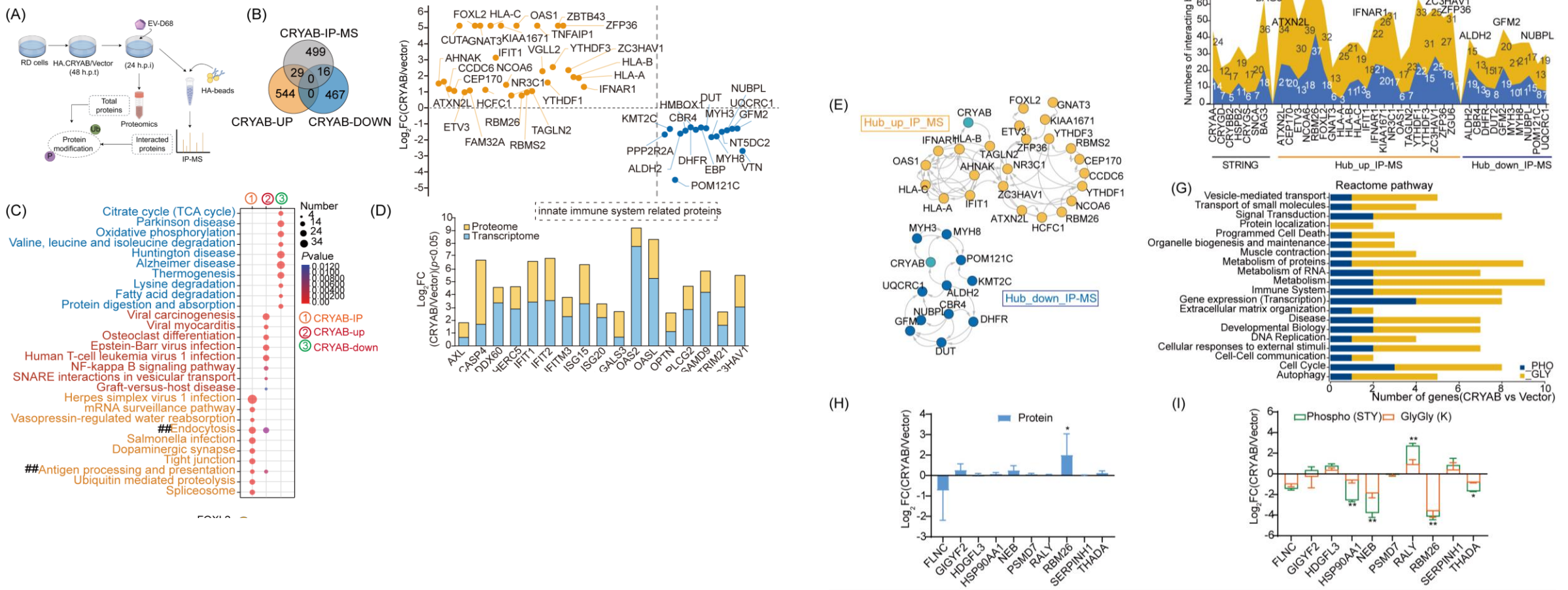
①Upon infection, CRYAB translocates from the cytoplasm to the nucleus. CRYAB overexpression alleviated cytopathic effects, reduced cell death, and induced nuclear condensation.

②CRYAB overexpression led to nuclear fragmentation and granule accumulation.

③ CRYAB overexpression regulated amino acid and nucleotide metabolism pathways.

CRYAB translocates to nucleus and regulates nucleotide metabolism during EV-D68 infection.

Key results overview-4



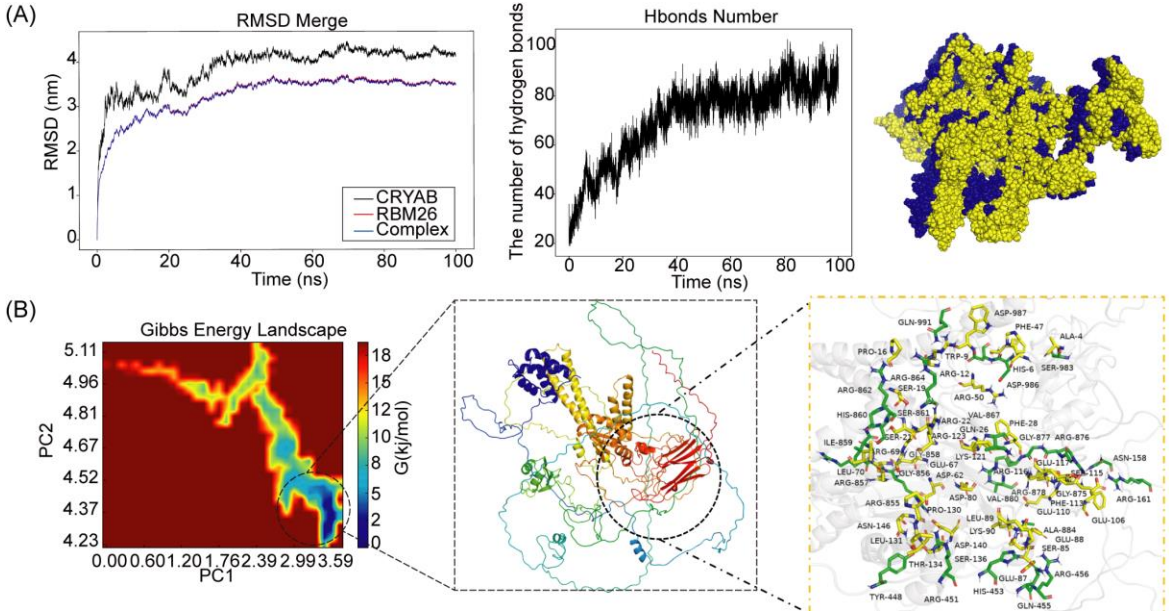
①CRYAB interacts with upregulated immune-related proteins.

②CRYAB overexpression significantly upregulated innate immune genes (e.g., OAS2, IFIT1) and showed broad interaction with related proteins.

③RBM26 showed a particularly strong interaction with CRYAB. CRYAB overexpression inhibited RBM26 ubiquitination-mediated degradation.

Multi-omics screening identified RBM26 as the downstream effector of CRYAB in regulating host immune response and nucleic acid pathways.

Key results overview-5

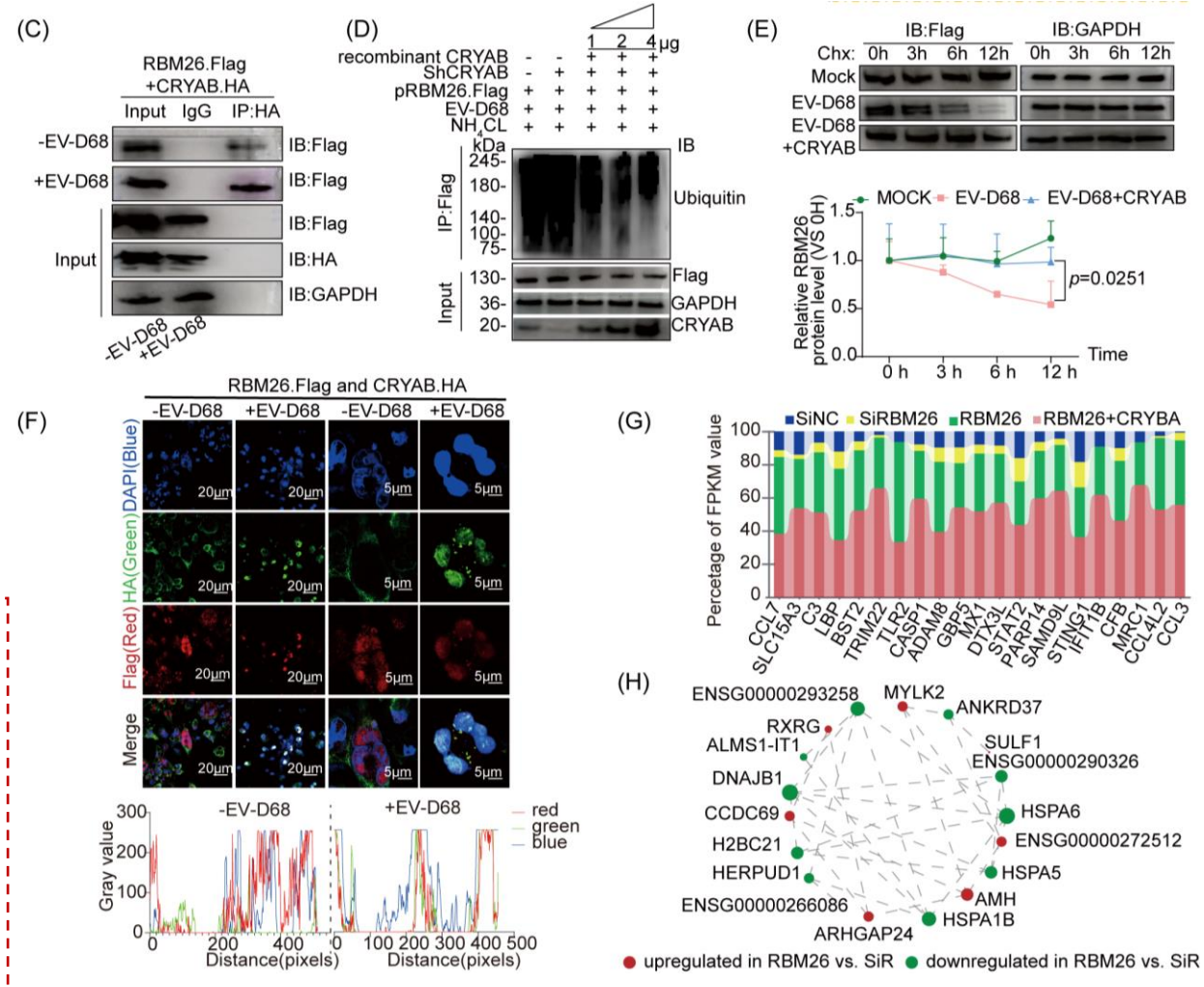


①EV-D68 infection enhanced this interaction. CRYAB stabilizes RBM26 by inhibiting its degradation.

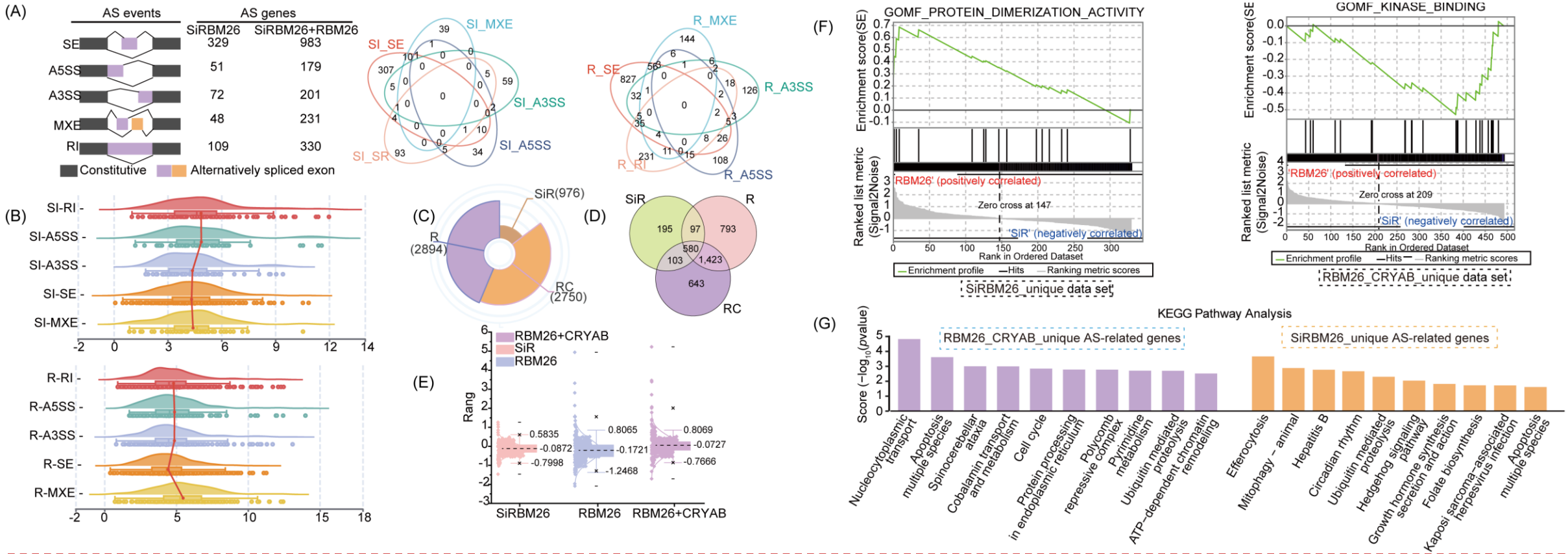
②Post-infection, CRYAB translocates to the nucleus and co-localizes with RBM26.

③ RBM26 and CRYAB co-regulate immune-related pathways, synergistically upregulating antiviral effectors (e.g., STAT2, GBP5, IFIT1B, MX1).

CRYAB promotes immune response by stabilizing RBM26 and enhancing the transcriptional activation of antiviral systems.



Key results overview-6



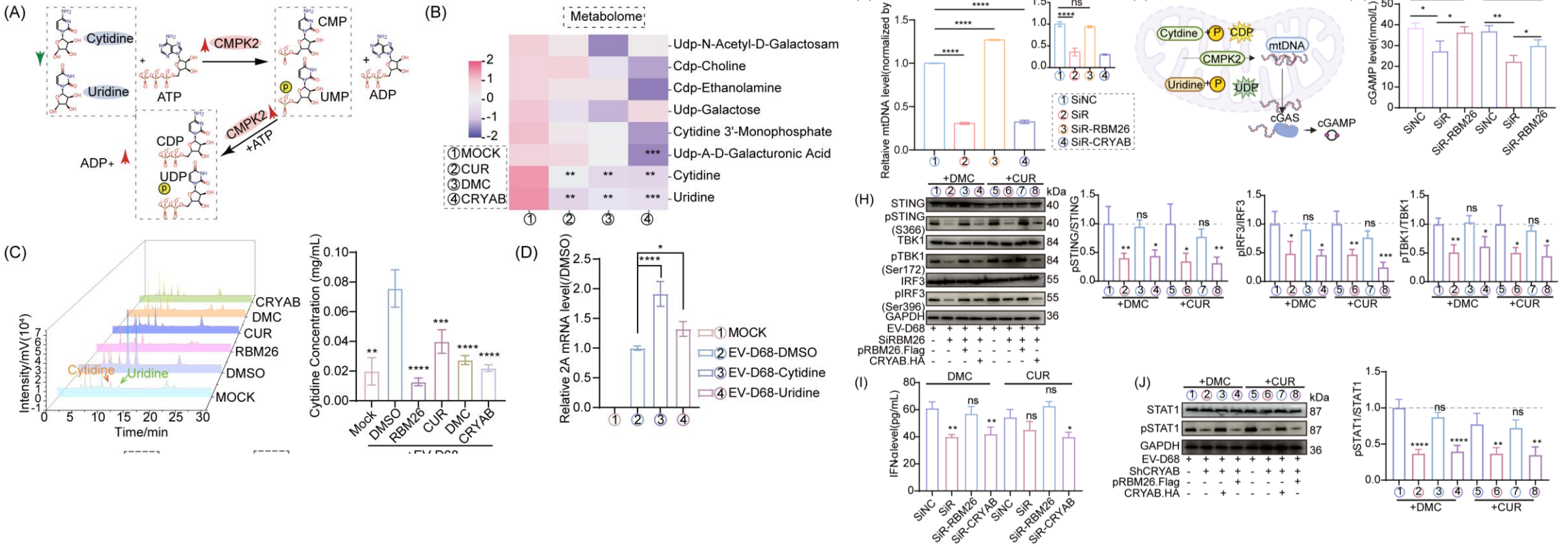
①RBM26 significantly enhanced global Alternative Splicing (AS) activity, particularly promoting Skip Exon (SE) events.

②Co-expression with CRYAB induced the most abundant AS types. KEGG and WGCNA analyses linked the co-expression group to nucleocytoplasmic transport and pyrimidine metabolism.

③Integrated multi-omics identified CMPK2 as significantly upregulated at both transcriptional and protein levels, acting as a downstream factor of RBM26.

CRYAB enhances RBM26-mediated alternative splicing. CMPK2 is a potential downstream regulatory factor of the CRYAB-RBM26 axis.

Key results overview-7



①RBM26 regulates the alternative splicing of CMPK2, enhancing its expression, further promoted by CRYAB co-expression.

②RBM26 and DMC/CUR treatment significantly reduced cytidine levels, counteracting the infection-induced increase.

③DMC/CUR or RBM26 re-expression restored mtDNA content, promoting STING-TBK1-IRF3 pathway (activation phase).

④CRYAB enhanced DMC/CUR-mediated activation of STAT-ISGs pathway during infection (effector phase).

DMC/CUR regulate the IFN-I response via the CRYAB-RBM26 axis. RBM26 initiates the signal cascade, while CRYAB amplifies the subsequent immunometabolic response.

Summary

- This study constructs a complete "Natural Drug-Signal Protein-Immune Effector" evidence chain, achieving a mechanistic closed loop from metabolic regulation and protein homeostasis to signaling pathways;
- The "CRYAB–RBM26–Nucleic Acid Metabolism Reprogramming" molecular chain is the key downstream regulator for DMC/CUR to initiate the IFN-I pathway, providing a comprehensive mechanistic basis for their use as host-targeted antivirals;
- The research model of "extracting commonality from individuality" offers a new systematic approach for studying the mechanisms of single components and compound formulas in traditional medicine.。

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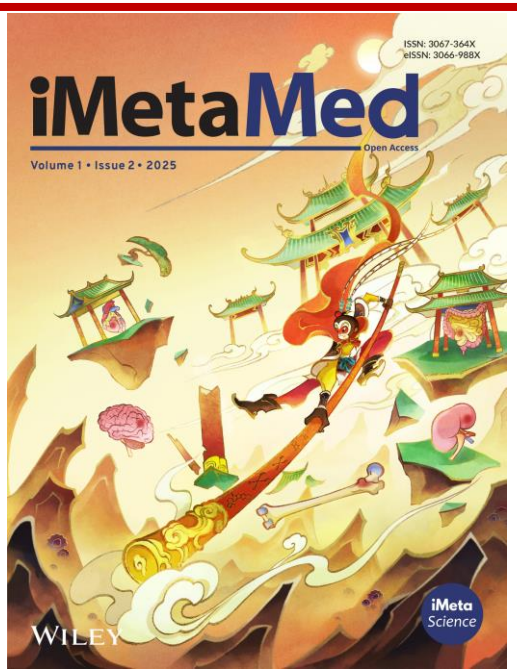

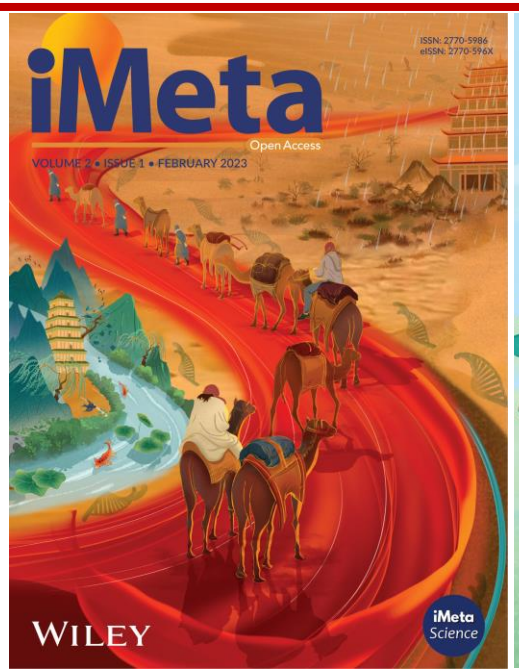

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