Homoharringtonine suppresses acute myeloid leukemia progression by orchestrating EWSR1 phase separation in an m^{6}A-YTHDF2-dependent mechanism

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Research Background and Objectives

Old Drug, New Use: The Therapeutic Potential of Homoharringtonine

01

Initial Approval (CML Treatment)

Homoharringtonine (HHT) was first approved for the treatment of chronic myeloid leukemia (CML). It is a natural alkaloid derived from plants and belongs to the class of natural biological compounds.

02

New Discovery (AML Efficacy)

Recent preclinical studies and early clinical trials have revealed that HHT exhibits remarkable therapeutic potential and antileukemic activity against acute myeloid leukemia (AML).

03

Synergistic Effects

When combined with agents such as arsenic trioxide (ATO) or all-trans retinoic acid (ATRA), HHT produces significant synergistic effects, offering new combinational strategies for AML treatment.

Key Scientific Questions

Unclear Mechanism of Action

The molecular mechanisms by which HHT exerts its antileukemic effects in AML remain largely unknown.

Lack of Target Identification

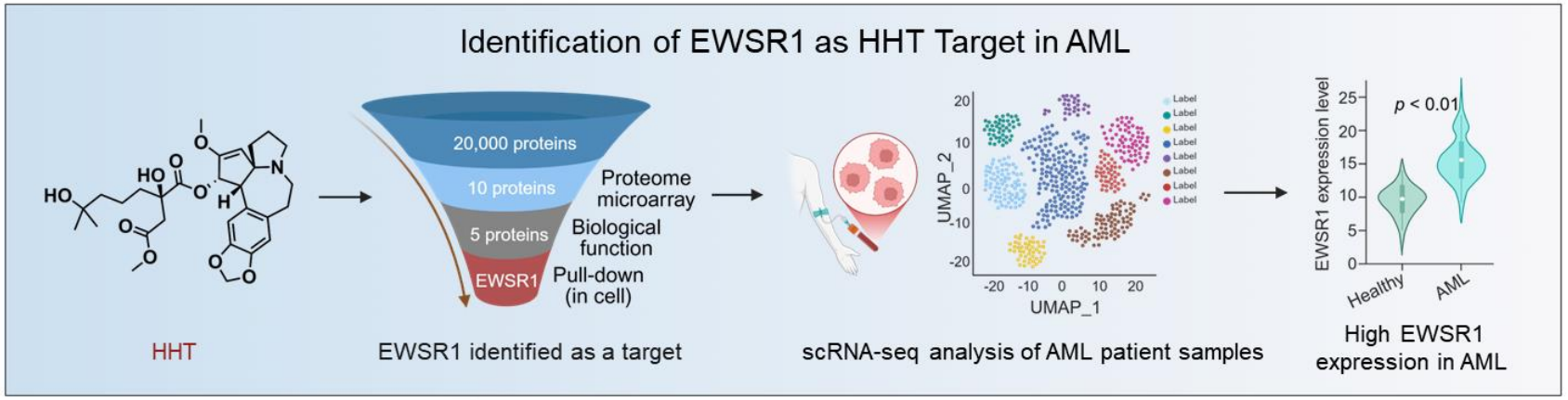
There is a lack of systematic studies revealing the interacting partners of HHT and key oncogenic proteins in AML.

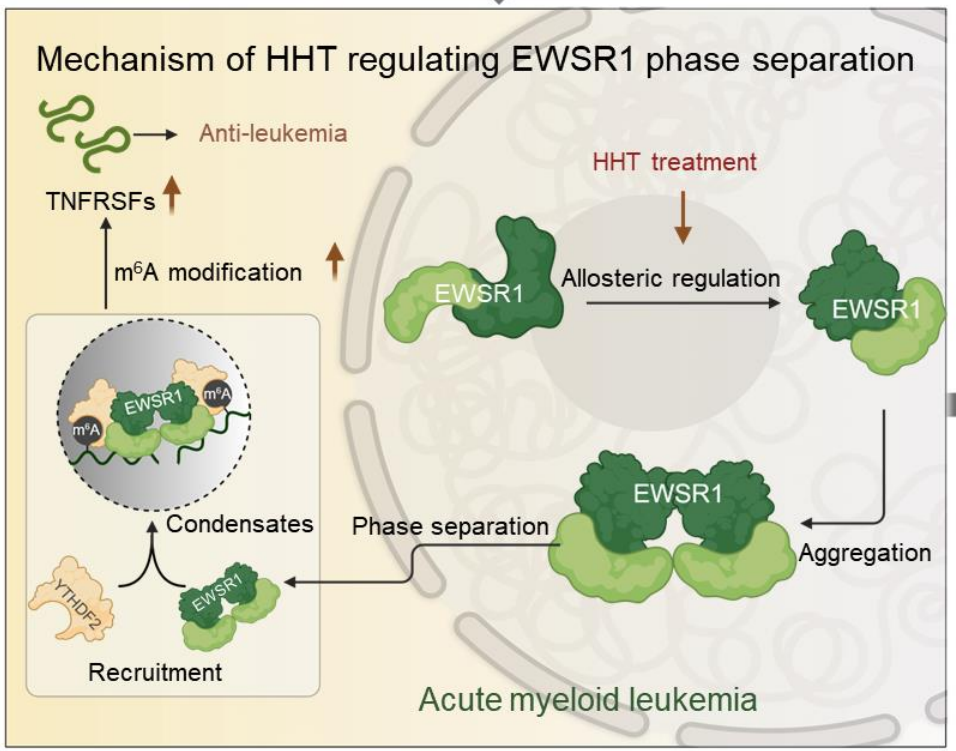
Unknown Signaling Pathways

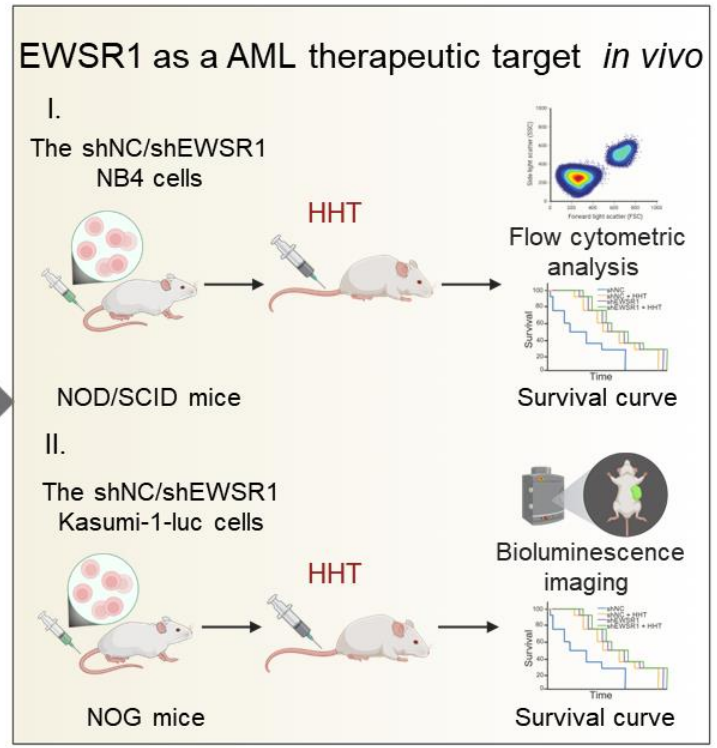
How HHT modulates malignant phenotypes and survival signaling in AML cells remains to be elucidated.

Clarifying these issues will optimize HHT therapy and identify new AML targets.

Highlights







- EWSR1 is identified as the direct cellular target of homoharringtonine (HHT) in acute myeloid leukemia (AML) through integrative chemical proteomics.
- HHT binding induces an allosteric conformational switch in EWSR1, promoting phase separation and sequestration of the m^{6}A reader YTHDF2.
- EWSR1 functions as both a therapeutic effector of HHT and a predictive biomarker for treatment responsiveness in AML.

Results: EWSR1 is identified as a cellular target of HHT in AML

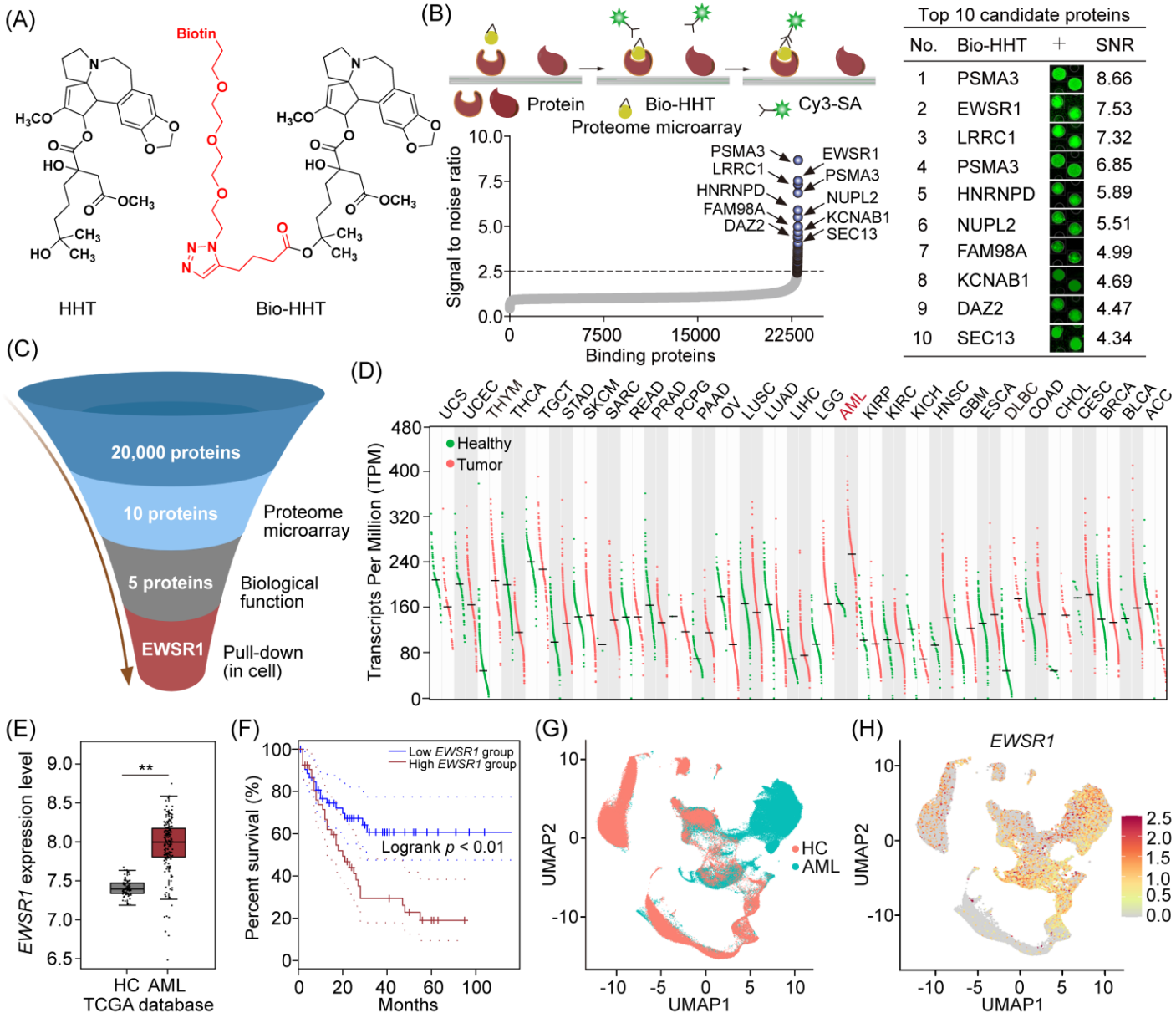


Figure 1. *EWSR1* is identified as a cellular target of homoharringtonine (HHT).

Results: EWSR1 is identified as a cellular target of HHT in AML

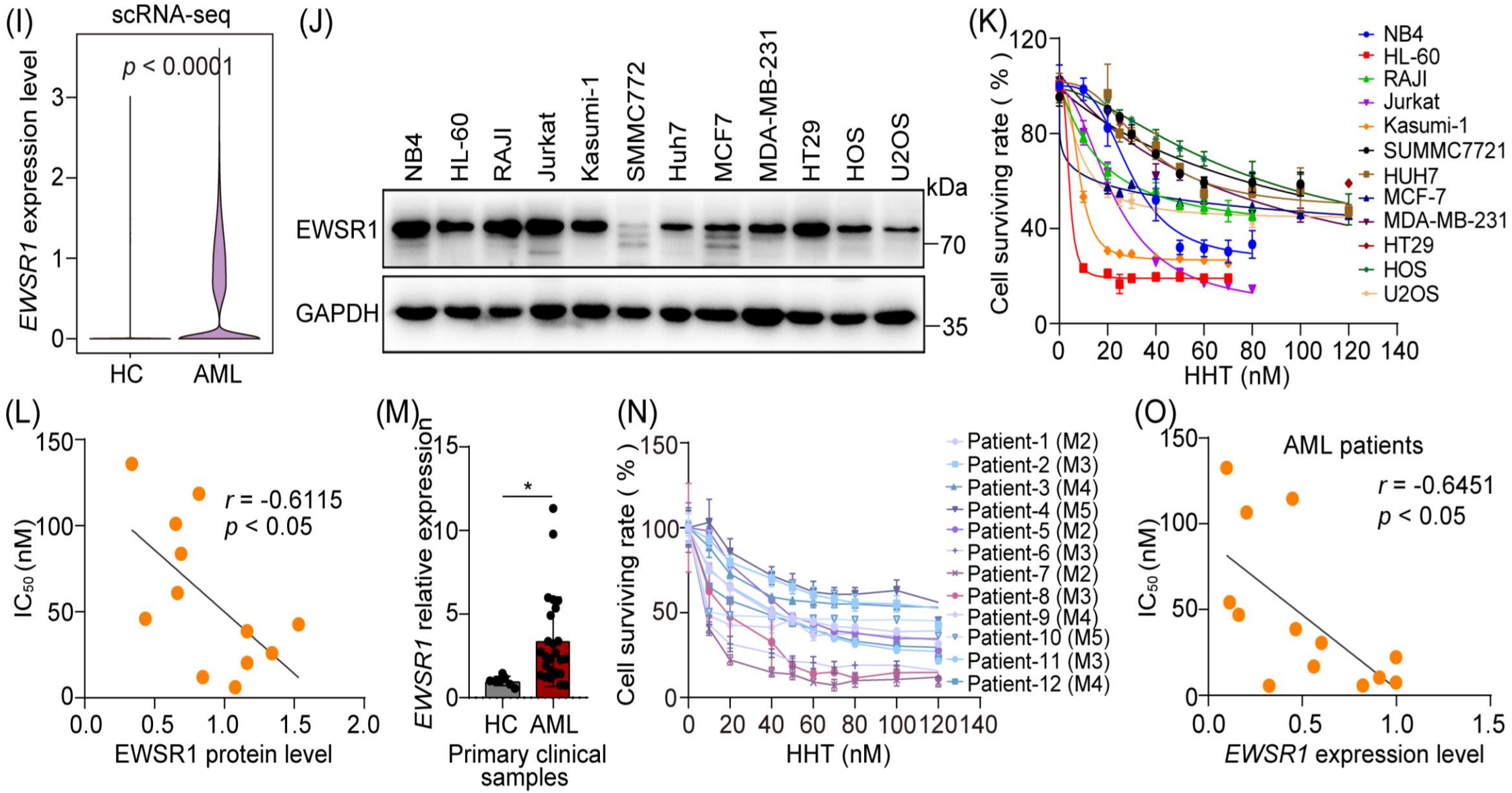


Figure 1. *EWSR1* is identified as a cellular target of homoharringtonine (HHT).

Results: RNA recognition motif of EWSR1 mediates HHT binding

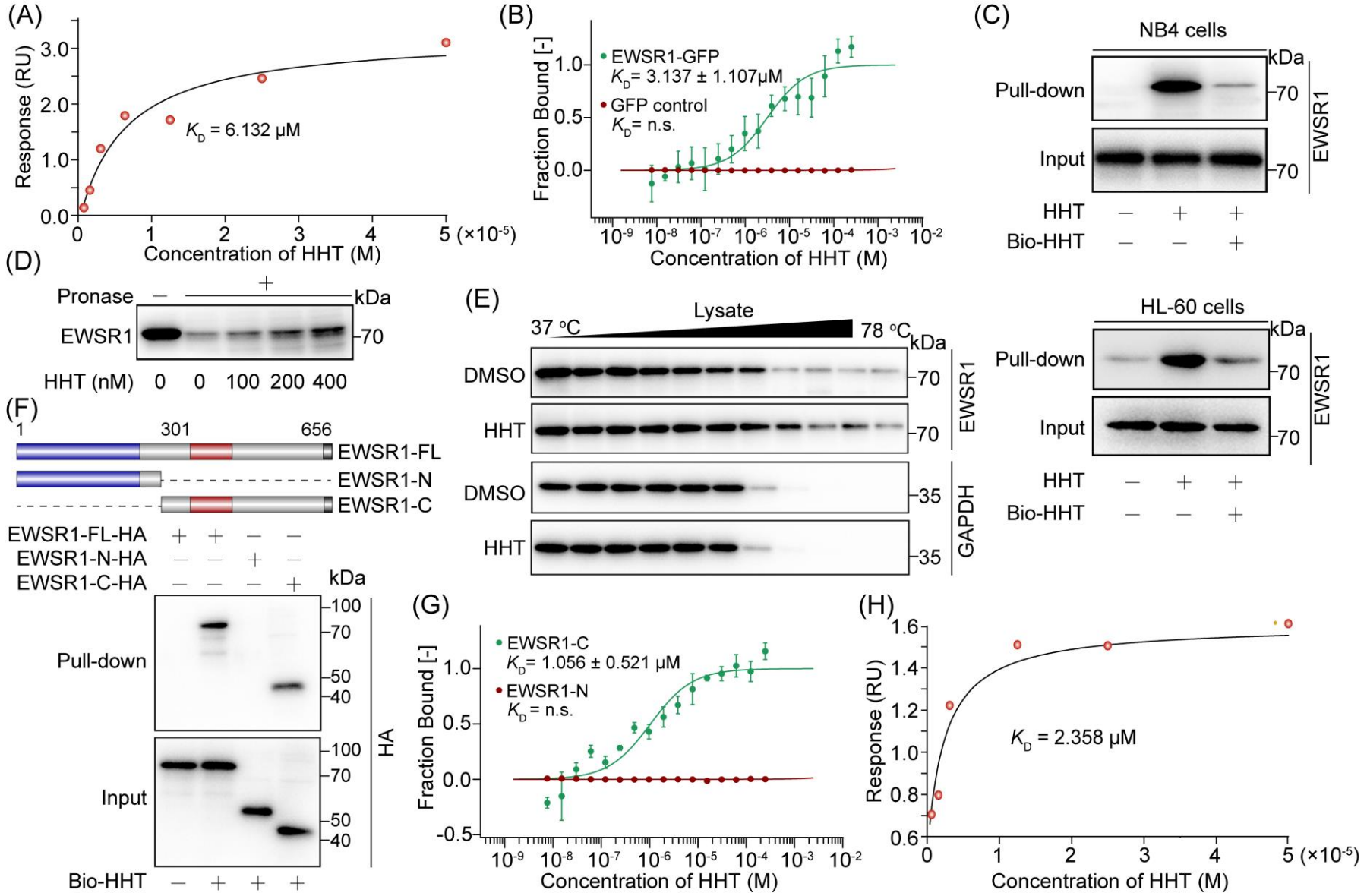
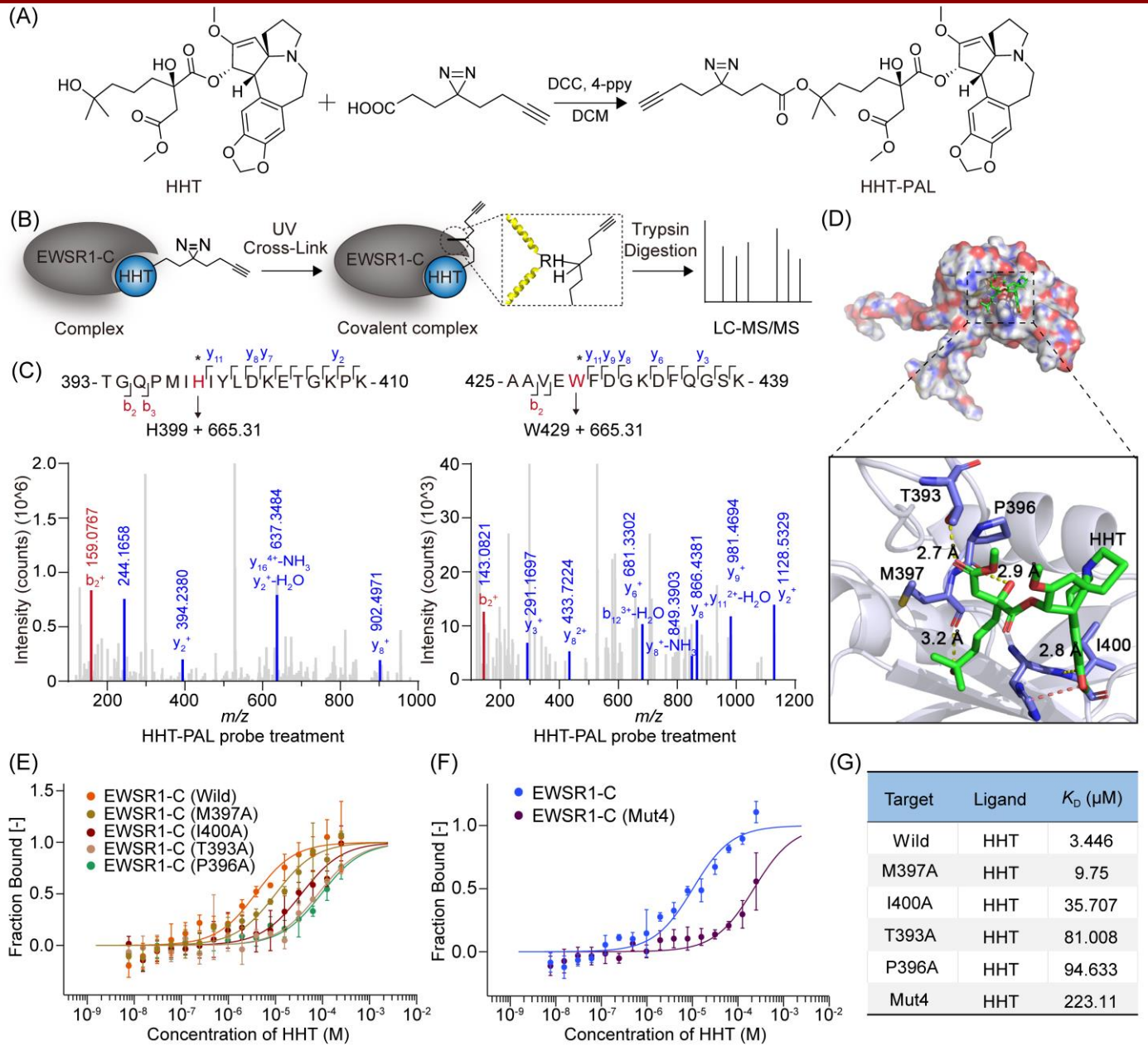


Figure 2. HHT binds the RNA recognition motif of EWSR1.

Results: HHT binds the RNA recognition motif of EWSR1 through hydrogen bonds



Target	Ligand	K_D (μM)
Wild	HHT	3.446
M397A	HHT	9.75
I400A	HHT	35.707
T393A	HHT	81.008
P396A	HHT	94.633
Mut4	HHT	223.11

Figure 3. HHT interacts with the RNA recognition motif through hydrogen bonds.

Results: HHT promotes the droplet formation of the EWSR1 protein

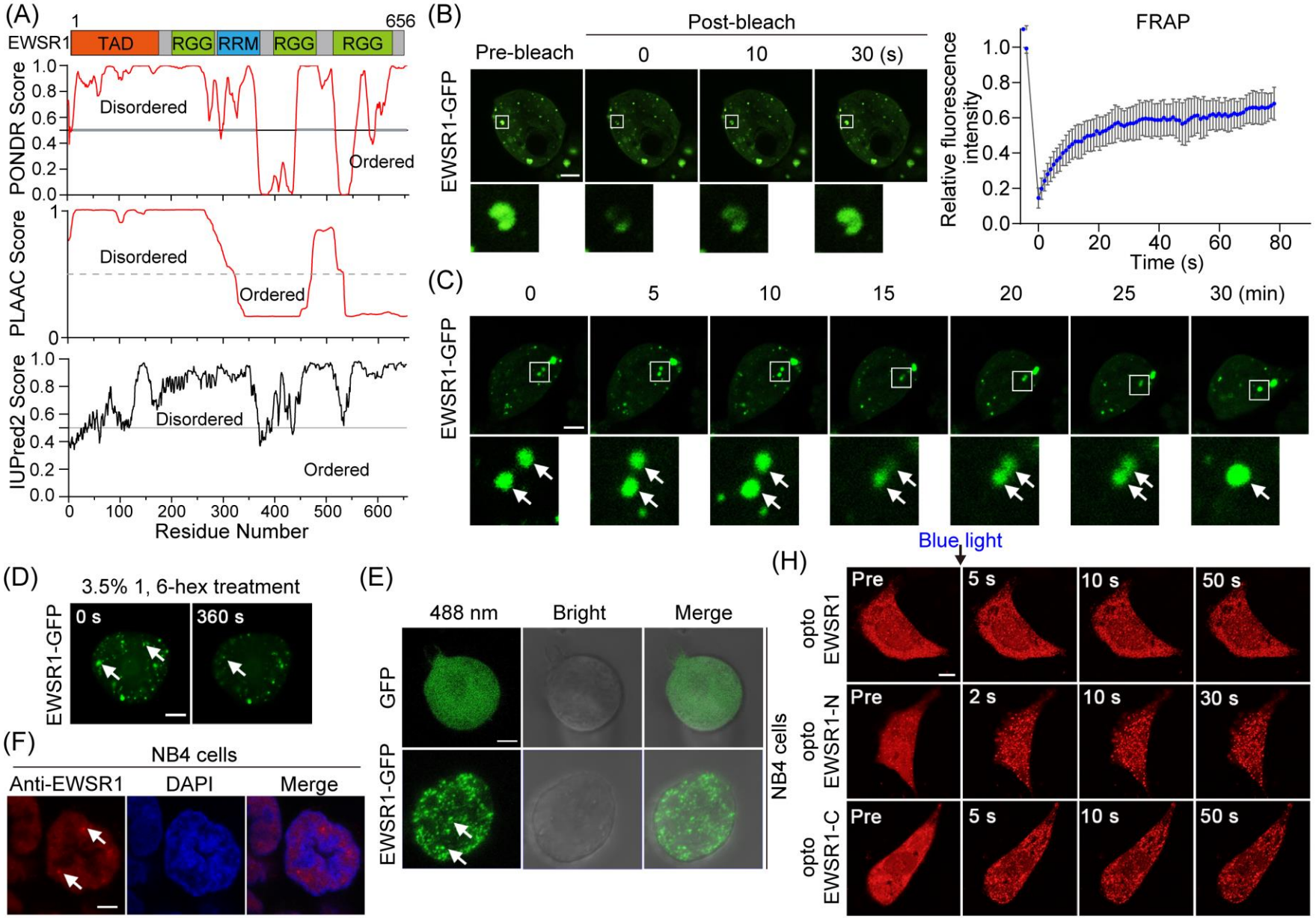


Figure 4. HHT promotes liquid-liquid phase separation of EWSR1 protein.

Results: HHT promotes the droplet formation of the EWSR1 protein

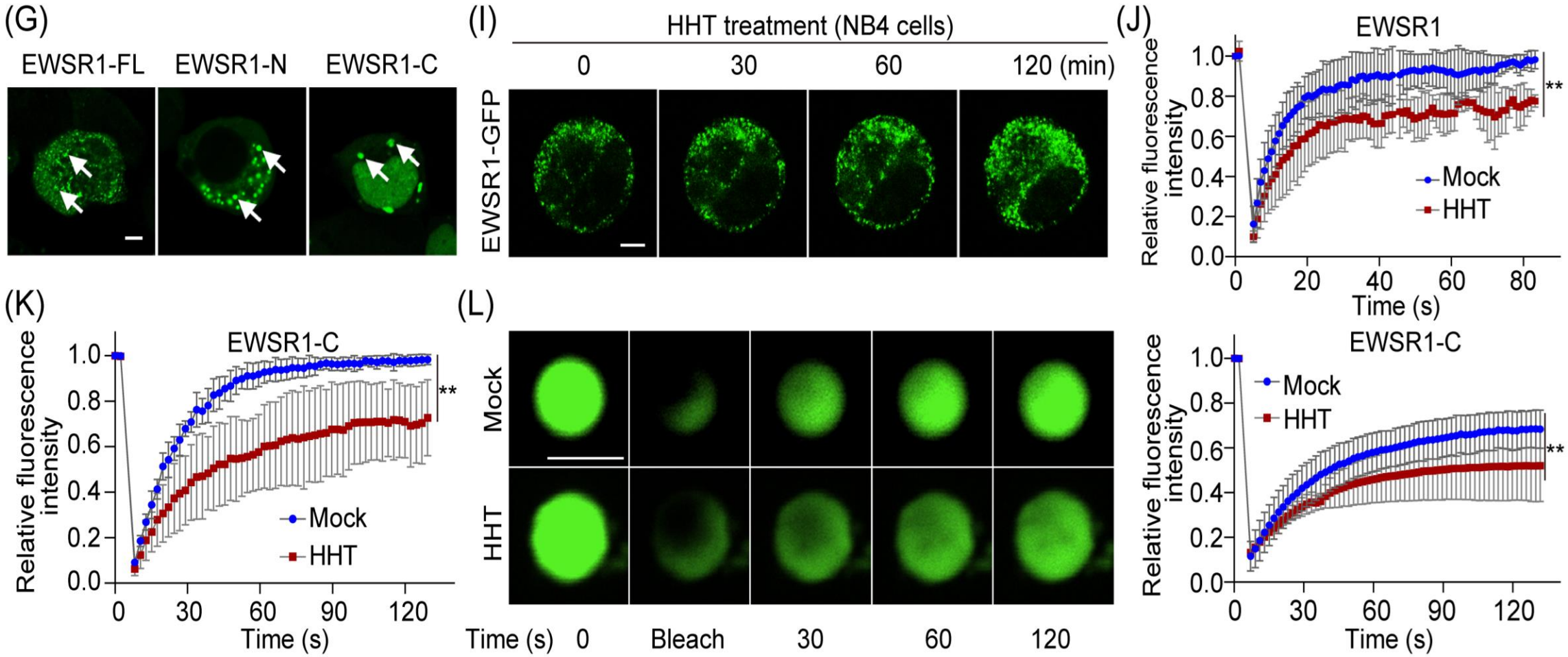


Figure 4. HHT promotes liquid-liquid phase separation of EWSR1 protein.

Results: HHT facilitates EWSR1 phase separation via an allosteric mechanism

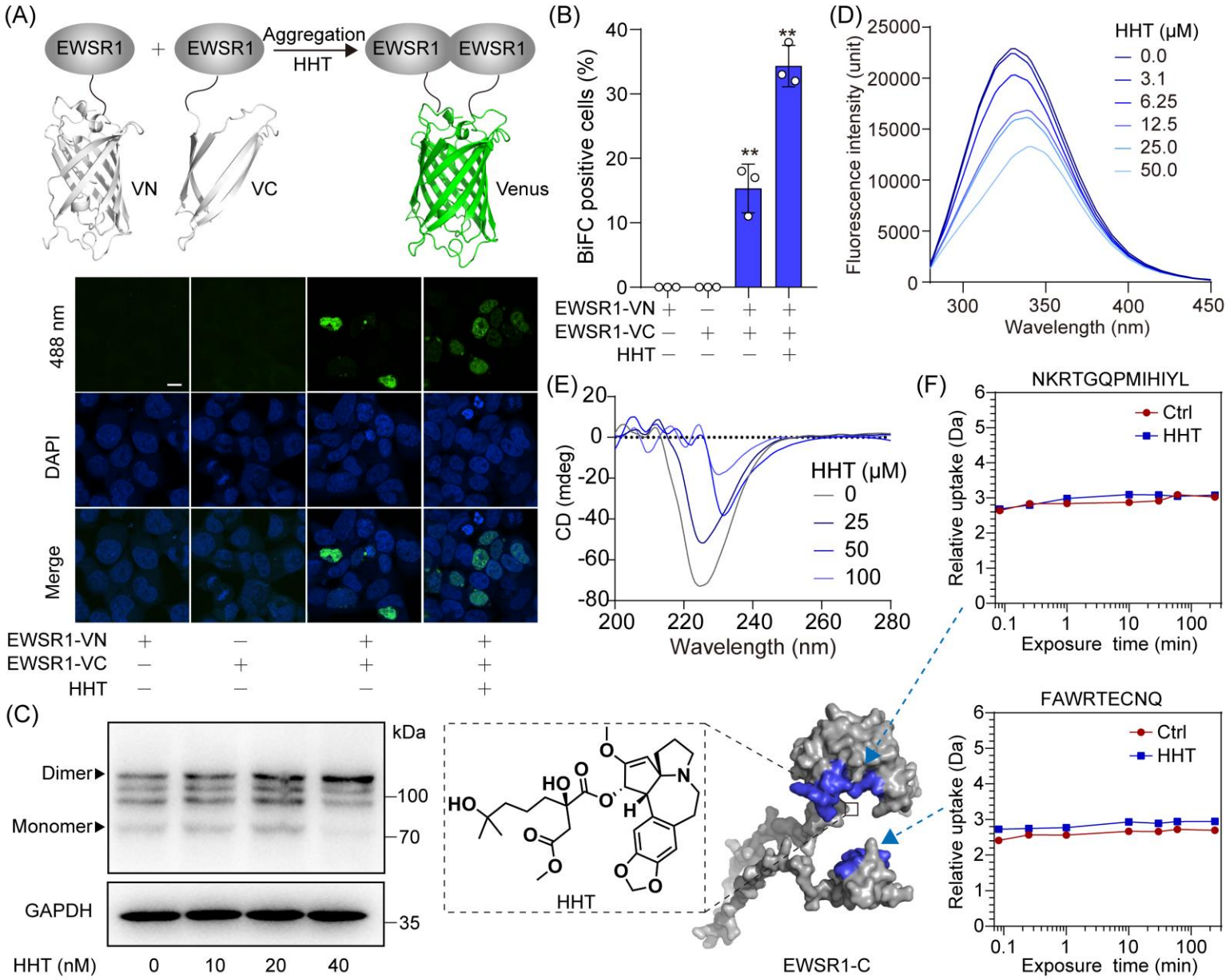


Figure 5. HHT facilitates EWSR1 phase separation via an allosteric regulation.

Results: HHT enhances EWSR1-YTHDF2 interaction to suppress m^{6}A recognition

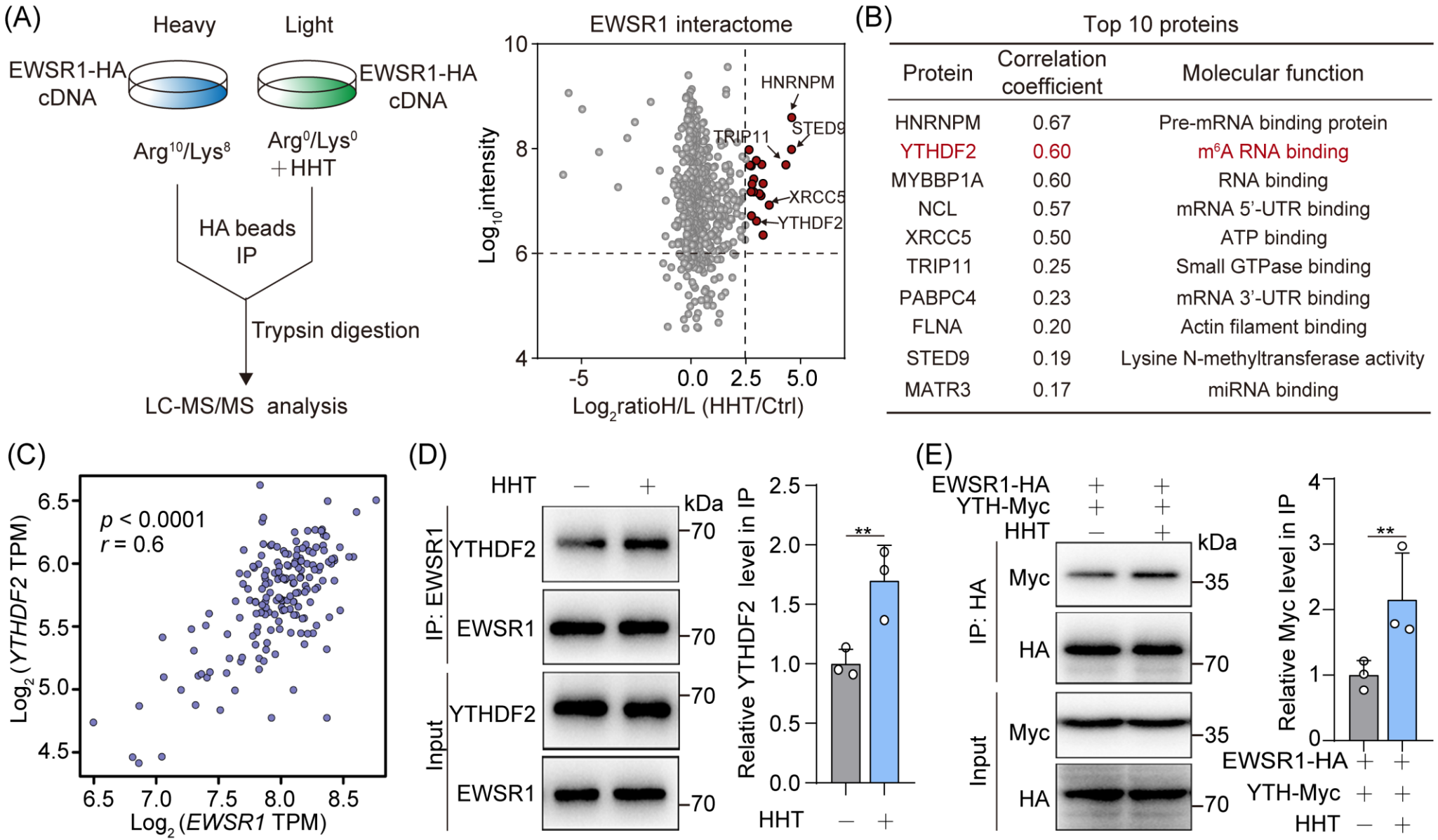


Figure 6. HHT strengthens EWSR1-YTHDF2 interaction, restricting m^{6}A recognition.

Results: HHT enhances EWSR1-YTHDF2 interaction to suppress m^{6}A recognition

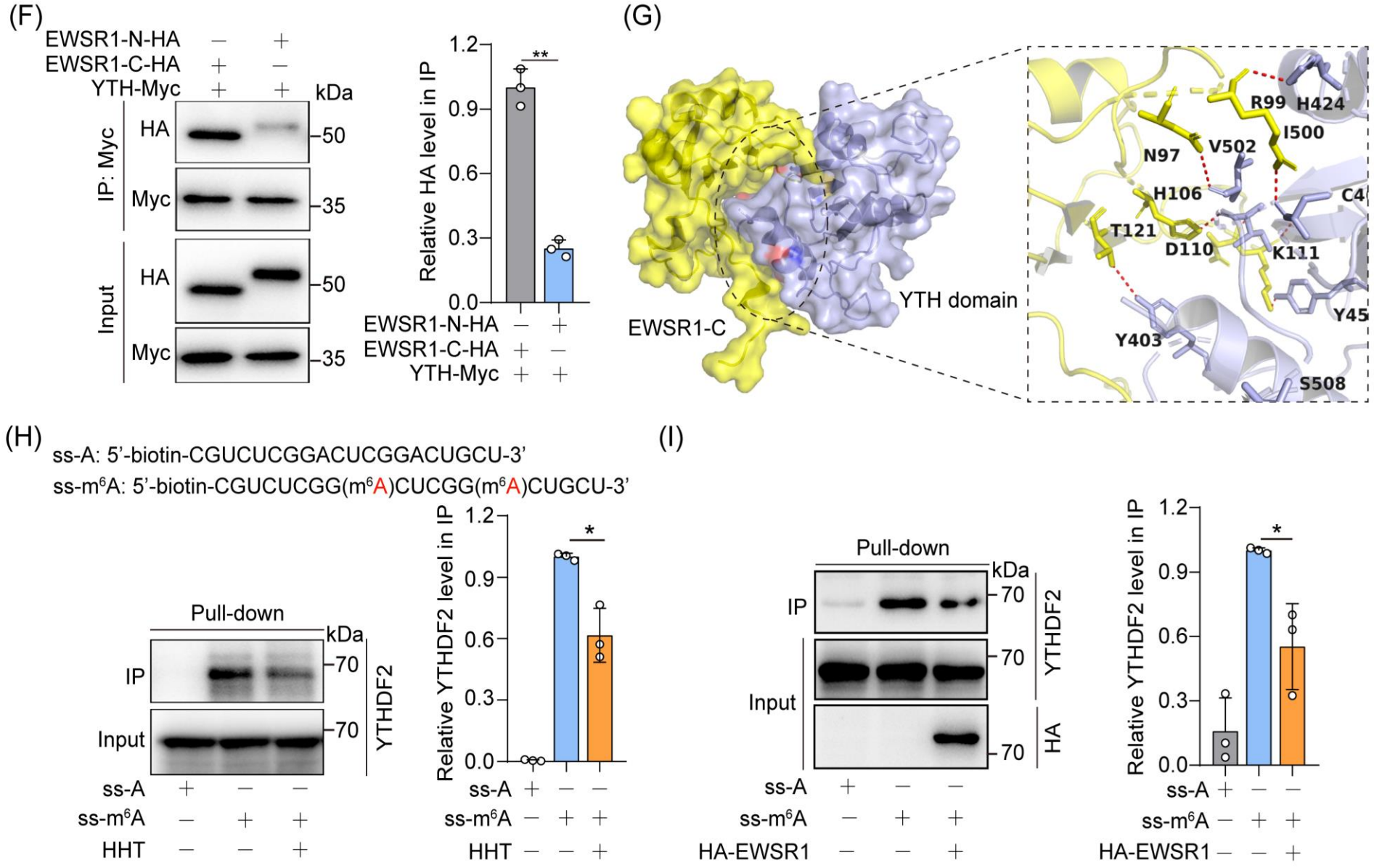


Figure 6. HHT strengthens EWSR1-YTHDF2 interaction, restricting m^{6}A recognition.

Results: HHT stabilizes m^{6}A-modified transcripts via EWSR1-YTHDF2 axis

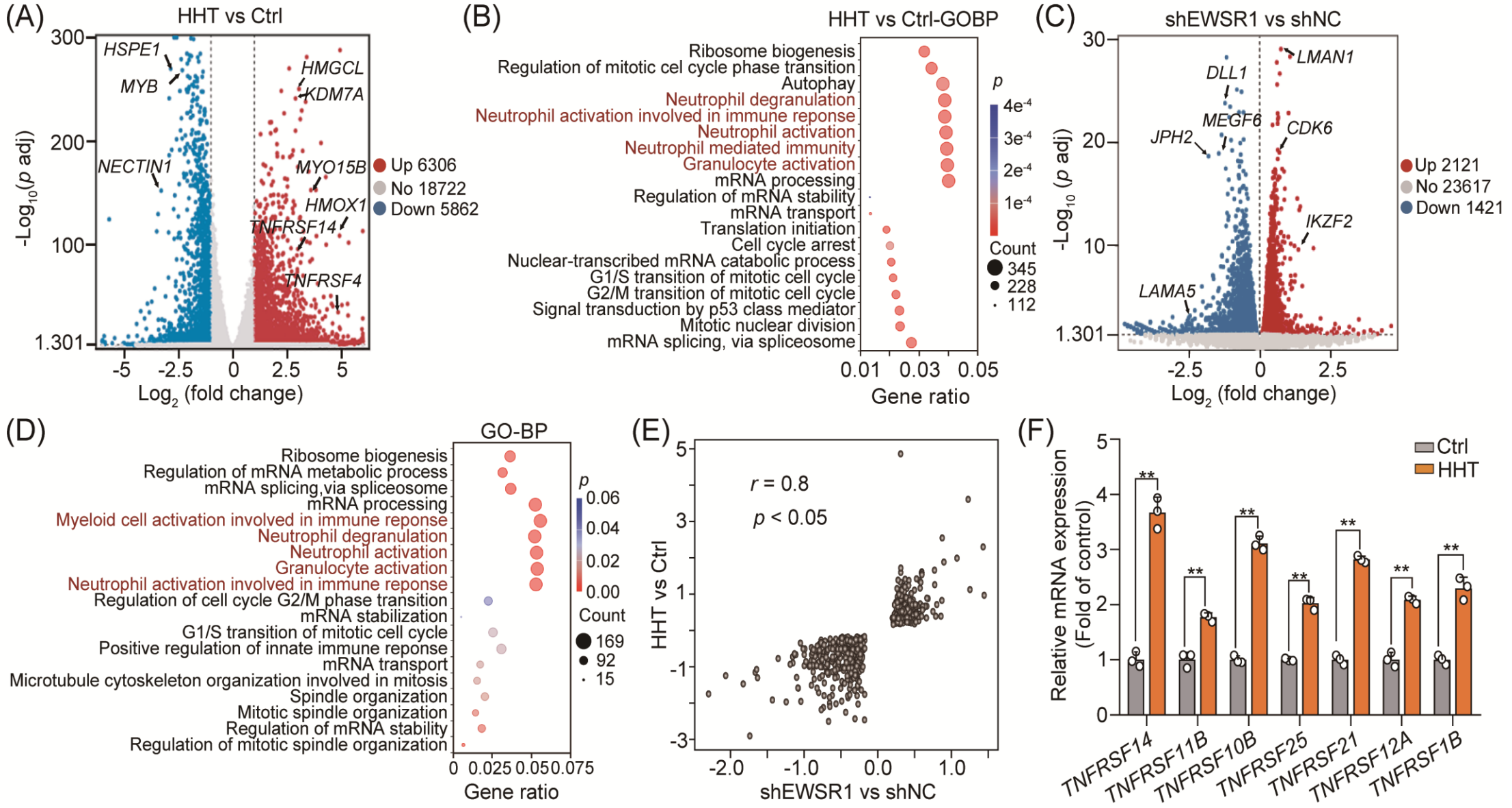


Figure 7. HHT modulates m^{6}A-modified RNA stability through the EWSR1-YTHDF2 axis.

Results: HHT stabilizes m^{6}A-modified transcripts via EWSR1-YTHDF2 axis

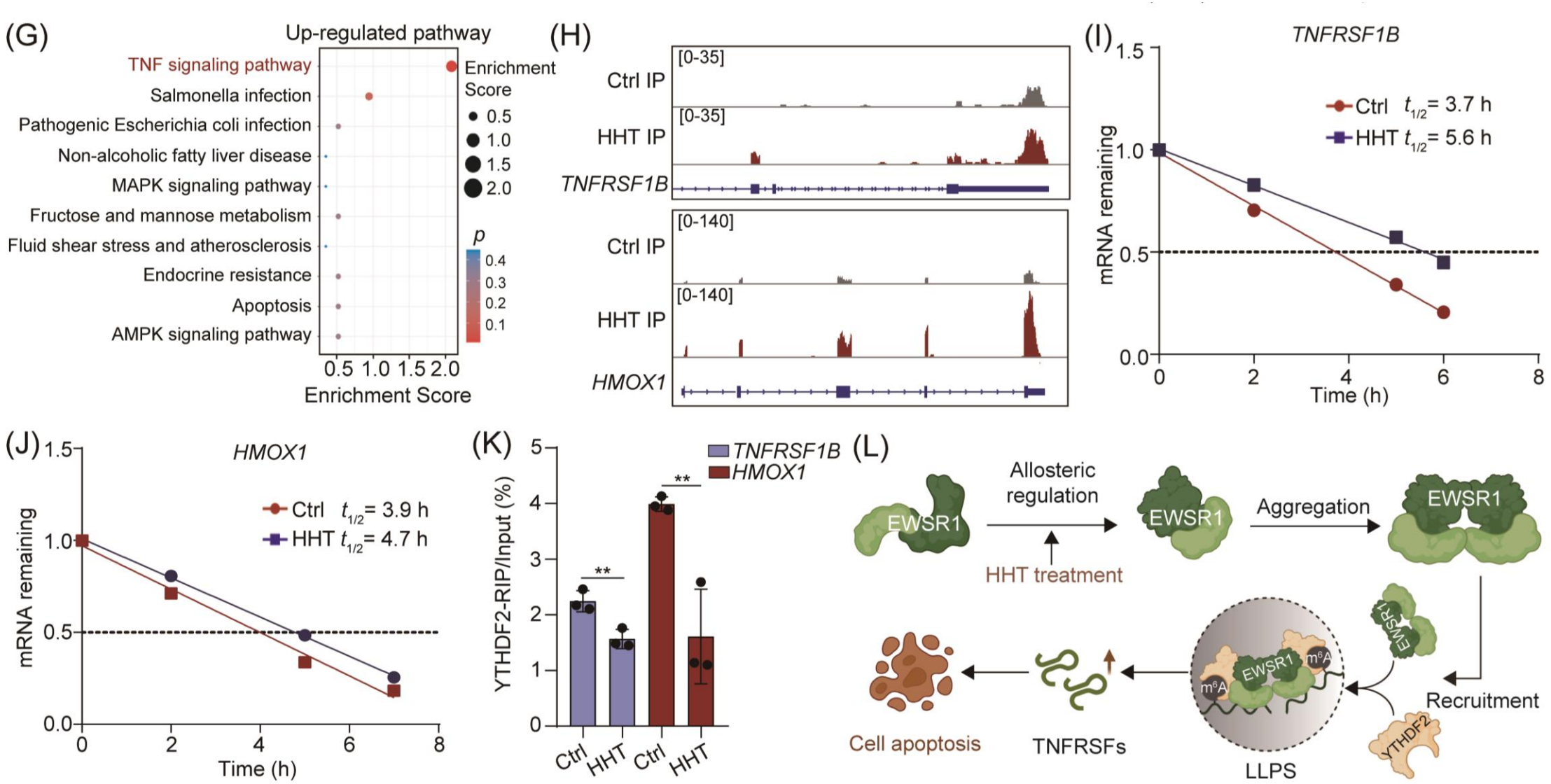


Figure 7. HHT modulates m^{6}A-modified RNA stability through the EWSR1-YTHDF2 axis.

Results: EWSR1 serves as a therapeutic target for AML *in vivo*

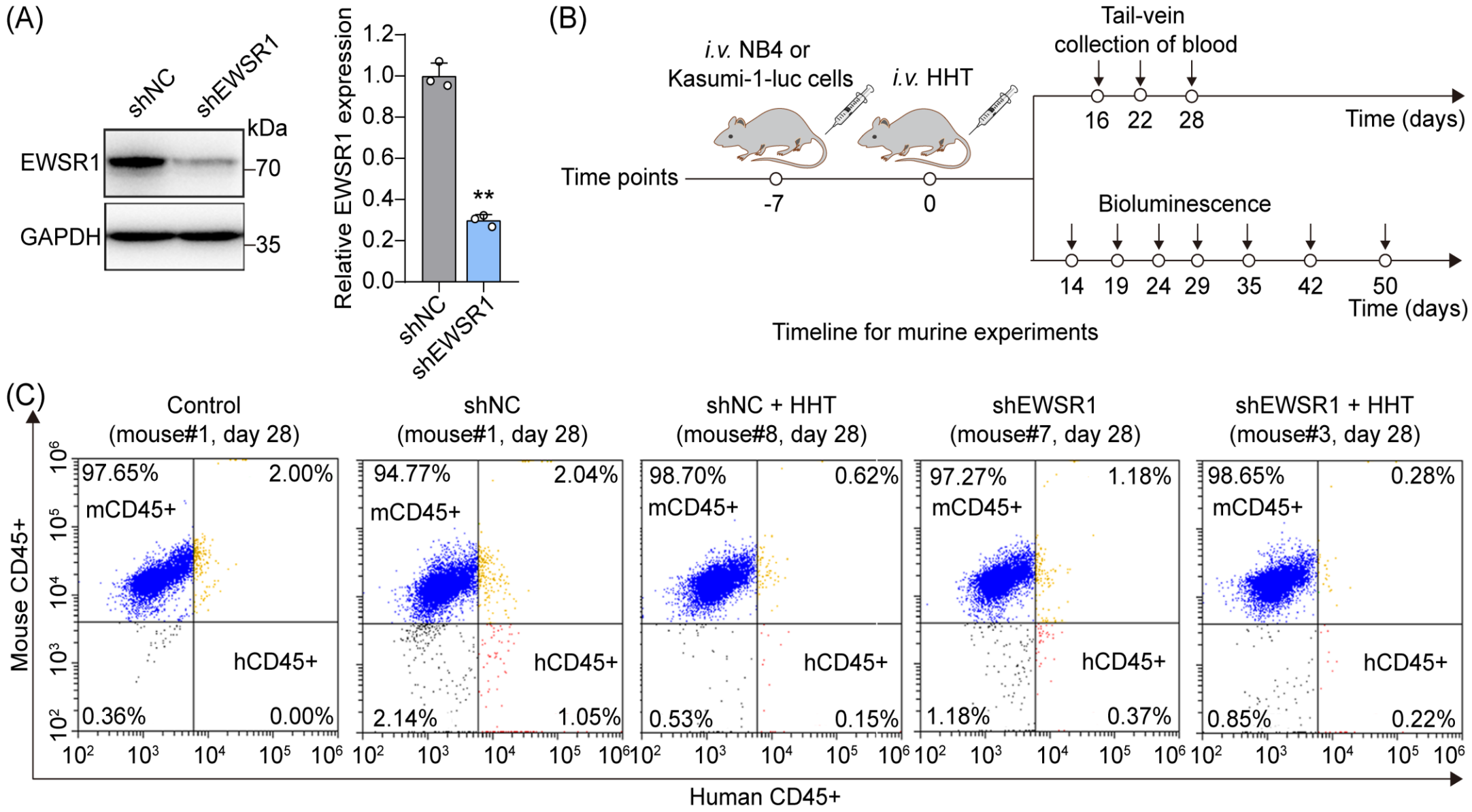


Figure 8. Targeting EWSR1 with HTT suppresses AML progression *in vivo*.

Results: EWSR1 serves as a therapeutic target for AML *in vivo*

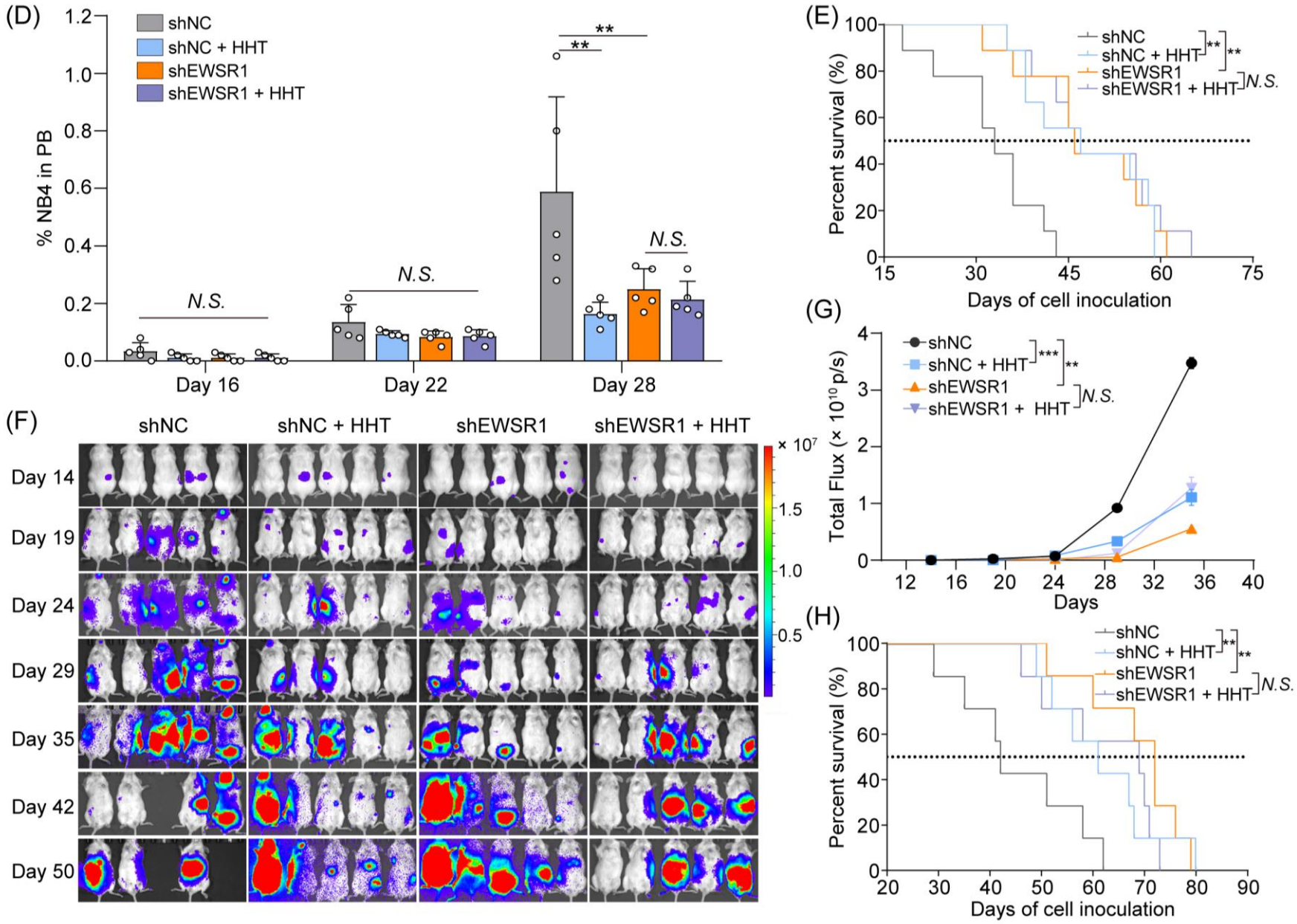


Figure 8. Targeting EWSR1 with HTT suppresses AML progression *in vivo*.

Summary

- EWSR1 is the direct cellular target of homoharringtonine (HHT) in AML.
- HHT induces an allosteric conformational switch that drives EWSR1 phase separation.
- EWSR1 condensates sequester YTHDF2 to suppress m^6A-dependent RNA decay.
- EWSR1 is required for HHT's anti-leukemic efficacy and predicts treatment responsiveness.

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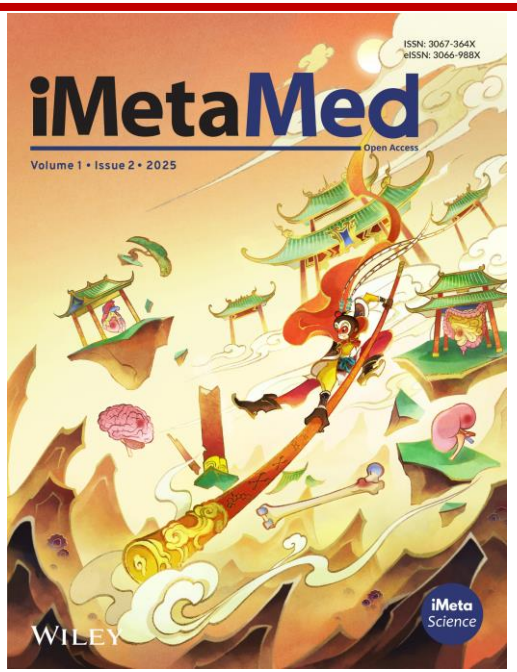

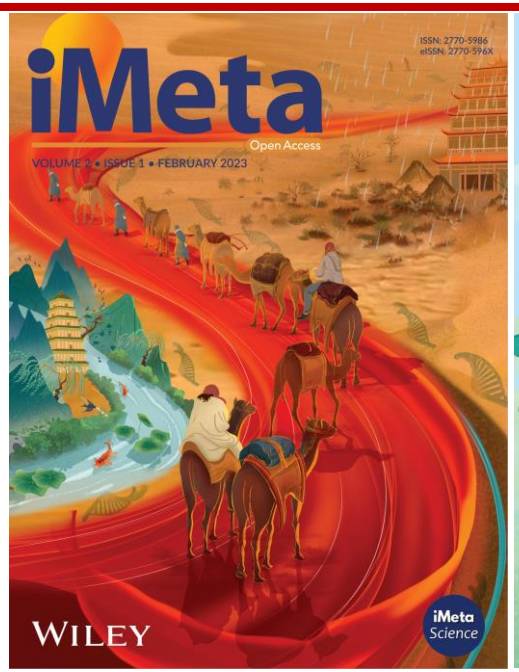

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