Protein modification with ISG15 blocks coxsackievirus pathology via antiviral and metabolic reprogramming

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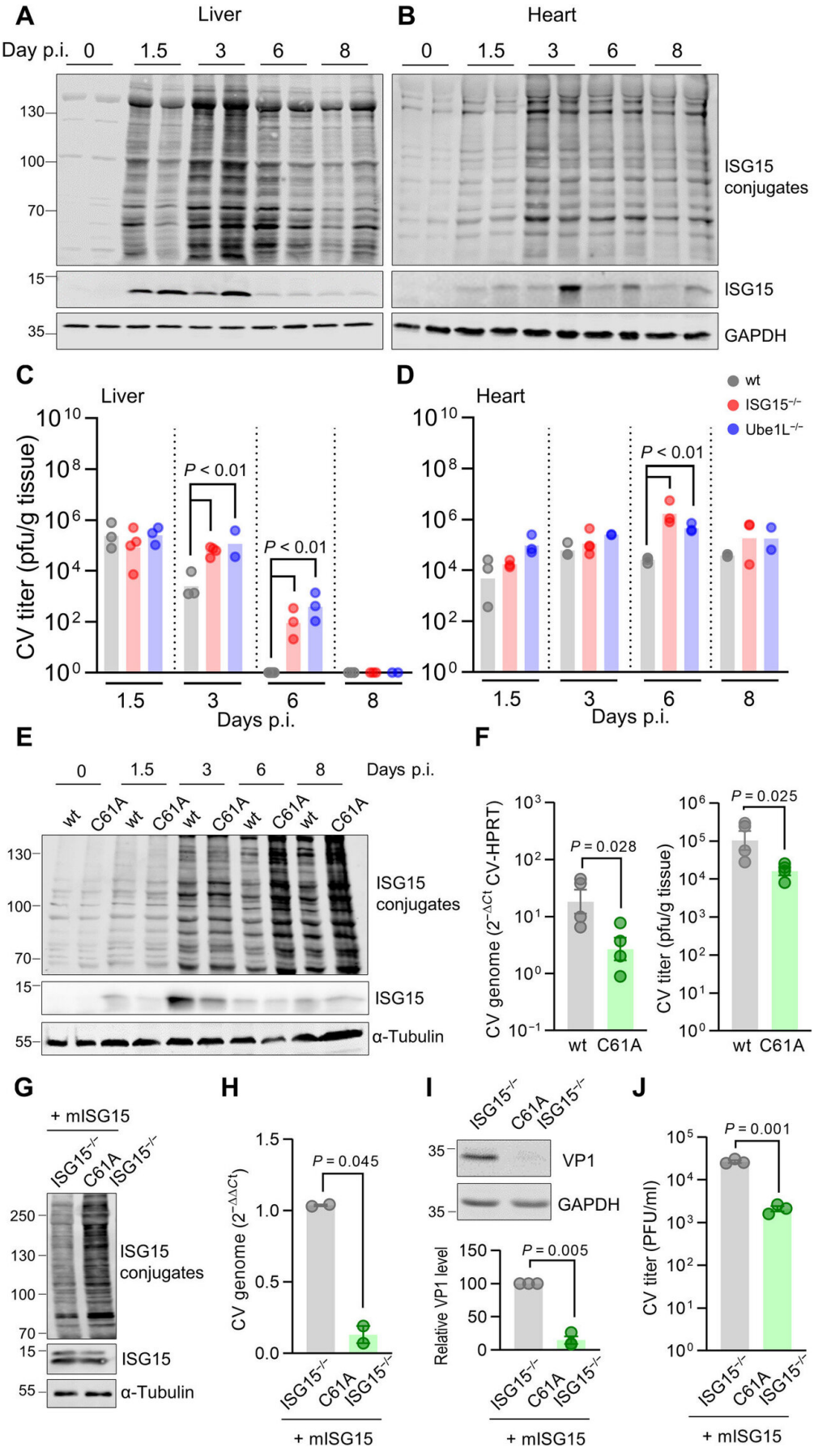
A
Liver
Day p.i. 0 1.5 3 6 8
130
100
70
15
35
ISG15 conjugates
ISG15
GAPDH
B
Heart
0 1.5 3 6 8
C
Liver
CV titer (pfu/g tissue)
P < 0.01
P < 0.01
1.5 3 6 8
Days p.i.
D
Heart
wt
ISG15−/−
Ube1L−/−
P < 0.01
1.5 3 6 8
Days p.i.
E
0 1.5 3 6 8 Days p.i.
wt C61A wt C61A wt C61A wt C61A wt C61A
130
100
70
15
55
ISG15 conjugates
ISG15
α-Tubulin
F
CV genome (2−ΔCt CV-HPRT)
P = 0.028
wt C61A
CV titer (pfu/g tissue)
P = 0.025
wt C61A
G
+ mISG15
ISG15−/− C61A ISG15−/−
250
130
100
70
15
55
ISG15 conjugates
ISG15
α-Tubulin
H
CV genome (2−ΔΔCt)
P = 0.045
ISG15−/− C61A ISG15−/−
+ mISG15
I
ISG15−/− C61A ISG15−/−
35
VP1
35
GAPDH
Relative VP1 level
P = 0.005
ISG15−/− C61A ISG15−/−
+ mISG15
J
CV titer (PFU/ml)
P = 0.001
ISG15−/− C61A ISG15−/−
+ mISG15

ISGylation suppresses CV titers at different phases of infection. Wild-type (wt), ISG15−/−, and Ube1L−/− mice were infected with 1 × 105 pfu of CV Nancy and sacrificed at the indicated points in time post infection (p.i.). Tissue from (A) liver and (B) heart of wild-type mice was subjected to Western blot analysis using an ISG15-specific antibody. Each lane represents tissue homogenates obtained from a different animal. (C and D) Infectious viral particles were quantified in the respective organs obtained from wild-type, ISG15−/−, and Ube1L−/− mice by plaque assay during CV infection. Each dot represents a different animal; data are summarized as median values. Student's t tests were conducted. P values of