a RNA-seq (Cohort 2, ICC)

Overall survival probability vs Months

$SAA1^{high}$ (red), $SAA1^{low}$ (cyan)

$P < 0.05$

Number at risk
	0	5	10	15	20	25
$SAA1^{high}$	4	3	2	2	1	1
$SAA1^{low}$	6	5	5	5	4	**3**

b RNA-seq (Cohort 2, ICC)

Overall survival probability vs Months

$SAA2^{high}$ (red), $SAA2^{low}$ (cyan)

$P < 0.05$

Number at risk
	0	5	10	15	20	25
$SAA2^{high}$	4	3	2	2	1	1
$SAA2^{low}$	6	5	5	5	4	**3**

c Multiplexed IF (Cohort 4, secondary liver cancer)

Overall survival probability vs Months

S/A^{high} (red), S/A^{low} (cyan)

$P < 0.05$

Number at risk
	0	10	20	30	40	50	60
S/A^{high}	8	3	1	0	0	0	0
S/A^{low}	18	10	7	4	3	2	1

d Correlation of SAAs expression

$R = 0.75$, $P < 0.001$

SAAs expression in paratumor tissue vs SAAs expression of the invasive zone

e IHC of paratumor tissue (Cohort 3, ICC)

Overall survival probability vs Months

$SAAs^{high}$ (red), $SAAs^{low}$ (cyan)

$P < 0.05$

Number at risk
	0	50	100	150
$SAAs^{high}$	84	18	1	1
$SAAs^{low}$	9	2	1	0

f RNA-seq of paratumor tissue (Cohort 5, HCC)

Overall survival probability vs Months

$SAA1^{high}$ (red), $SAA1^{low}$ (cyan)

$P < 0.001$

Number at risk
	0	10	20	30	40	50
$SAA1^{high}$	30	26	18	11	7	0
$SAA1^{low}$	129	121	102	92	54	0

$SAA2^{high}$ (red), $SAA2^{low}$ (cyan)

$P < 0.001$

Number at risk
	0	10	20	30	40	50
$SAA2^{high}$	45	40	26	18	13	0
$SAA2^{low}$	114	107	94	85	48	0

g Protein expression (Cohort 5, HCC)

Overall survival probability vs Months

$SAAs^{high}$ (red), $SAAs^{low}$ (cyan)

$P < 0.01$

Number at risk
	0	10	20	30	40	50
$SAAs^{high}$	41	37	25	17	11	0
$SAAs^{low}$	118	110	95	86	50	0

h Relative expression of *Saa1* and *Saa2*

Saa1 (filled), *Saa2* (open)

pAAV.Con vs pAAV.Saas-Sh

*** ***

j CRLM model

Multiplexed IF : ARG1 (orange) SAAs (cyan) F4/80 (green) CD206 (magenta) DAPI (blue)

Multiplexed IF staining — pAAV.Con | pAAV.Saas-Sh — 200 μm, 50 μm

▶ SAAs⁺ARG1⁺ hepatocyte
▶ F4/80⁺ marcophage
▶ F4/80⁺ CD206⁺ macrophage

i SAAs concentration (ng/ml)

Medium control | Hepatocyte supernatant (pAAV.Con) | Hepatocyte supernatant (pAAV.Saas-Sh)

*** ***

k Cell subtype:
- F4/80⁺ marcophage (green)
- F4/80⁺ CD206⁺ macrophage (orange)
- SAAs⁺ARG1⁺ hepatocyte (blue)

HCC model — ln(number of cells) vs Distant / -750~-500 μm / -500~-250 μm / -250~0 μm (Tumor), Border, 0~250 μm / 250~500 μm / 500~750 μm / Distant (Paratumor)

CRLM model — ln(number of cells) vs Distant / -750~-500 μm / -500~-250 μm / -250~0 μm (Tumor), Border, 0~250 μm / 250~500 μm / 500~750 μm / Distant (Paratumor)

Supplementary information, Fig. S10. High SAAs expression in damaged hepatocytes in the invasive zone correlates with a poor prognosis in patients with liver cancer. (a-b) Overall survival (OS) curves of 10 patients with ICC from Validation Cohort 2 grouped by the *SAA1* a. or *SAA2* b. expression level in margin areas based on the bulk RNA-seq data. **c.** OS curves of 26 patients with secondary liver cancer from Validation Cohort 4 grouped based on the SAAs/ARG1 ratio determined using multiplexed IF staining. **d.** Scatter diagram showing the correlations between the SAAs expression levels in the invasive zone and paratumor tissues determined by IHC staining in 93 ICC patients from Validation Cohort 3. **e.** OS curves of 93 patients with ICC from Validation Cohort 3, grouped by their relative expression levels of SAAs in paratumor tissues as determined by IHC staining. **f.** OS curves of 159 patients with HCC from Validation Cohort 5, grouped by the relative expression levels of *SAA1* and *SAA2* in the paratumor tissues as indicated by RNA-seq data. **g.** OS curves of 159 patients with HCC from Validation Cohort 5, grouped by their relative expression levels of SAAs in paratumor tissues based on proteomic data. **h.** Relative transcriptional expression levels of SAAs in the liver tissues of mice in pAAV9-Con group or pAAV9-*Saas*-Sh group. **i.** Secreted SAAs protein levels measured by mouse SAAs enzyme-linked immunosorbent assay (ELISA) kit in the supernatant of murine primary hepatocytes cultured for 12 hours of mice in pAAV9-Con group and pAAV9-*Saas*-Sh group. **j.** Multiplexed IF staining images shows the tumor ecosystem including hepatocyte (ARG1), SAAs$^+$ hepatocyte, macrophage (F4/80) and M2 macrophage (F4/80$^+$CD206$^+$ cells) in invasion zone from mouse CRLM model **k.** Quantification of macrophages, M2 macrophages and SAAs$^+$ hepatocytes in different layers of the invasive zone (1000 μm in normal length) from HCC models and CRLM models. The Log-rank test was used to analyze the data in panels **a-c**, **e-g**. Student's *t*-test was used to analyze the data in panel **h** and **k**. * represents $P < 0.05$; **, represents $P < 0.01$; ***, represents $P < 0.001$.