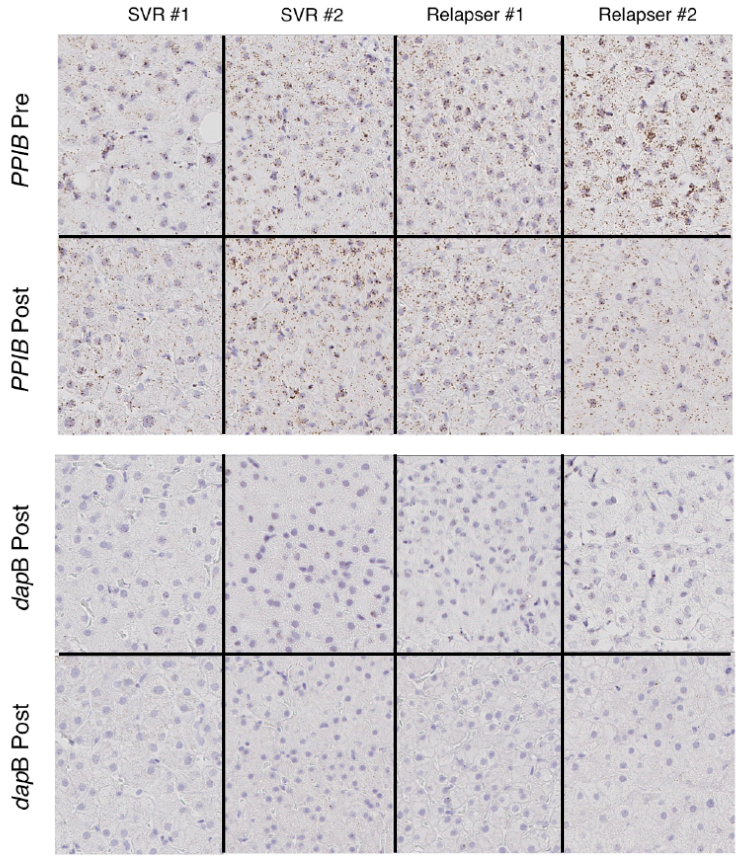
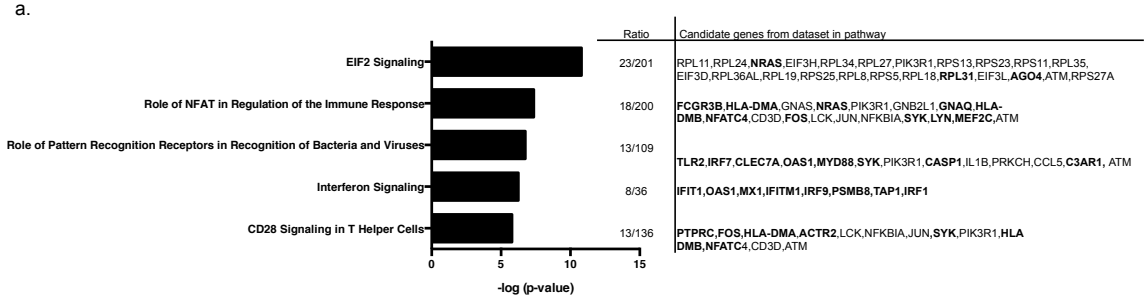
Supplementary Figures

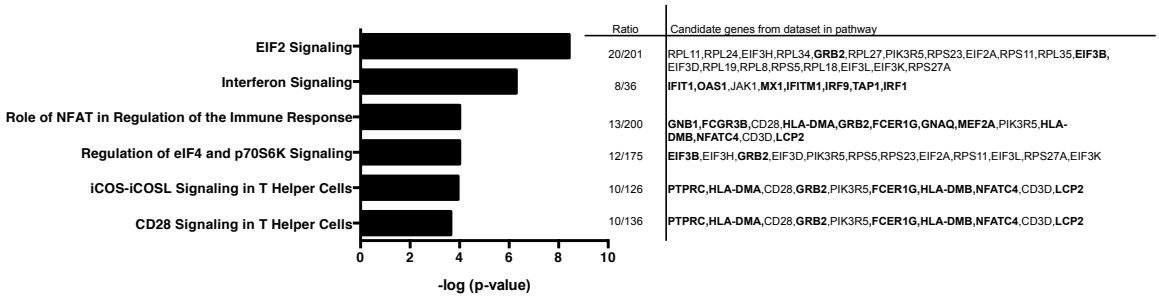


Supplementary Figure 1: Positive (*PPIB*) and negative (*dap*B) controls are shown for comparison to *IFI44 in situ* hybridization reported in Figure 2b.

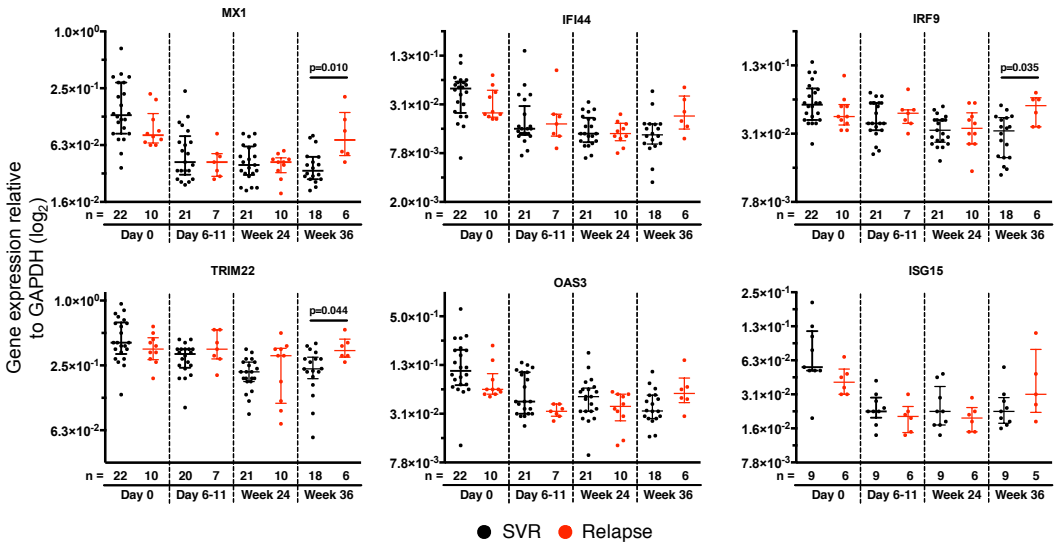
a.



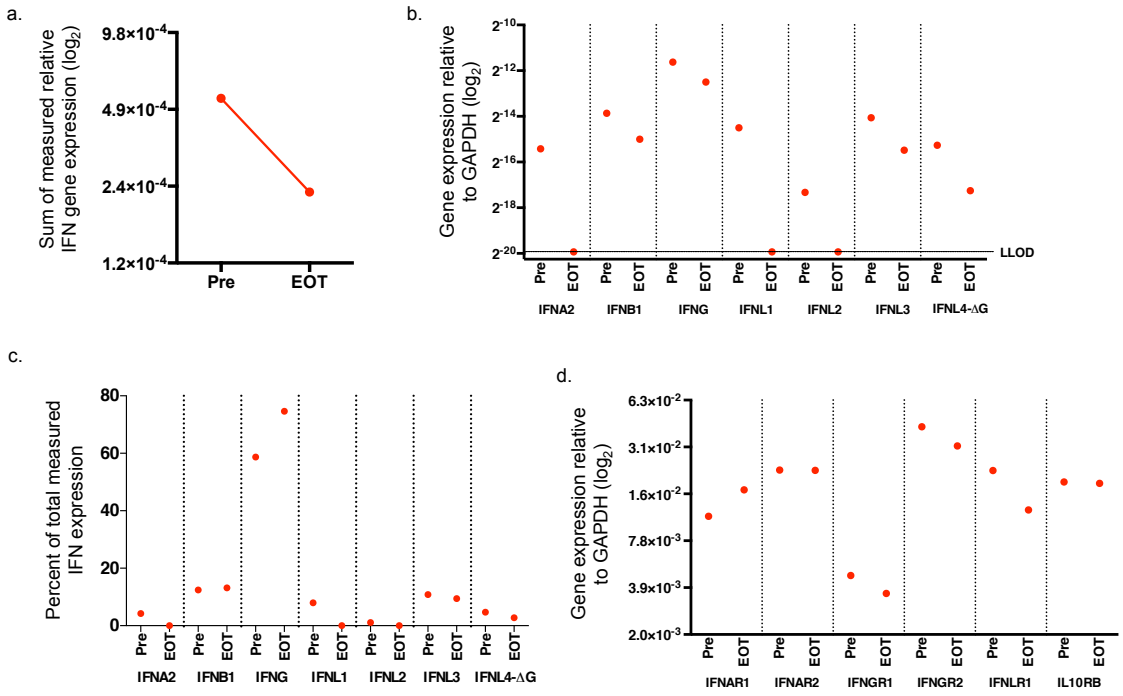
b.



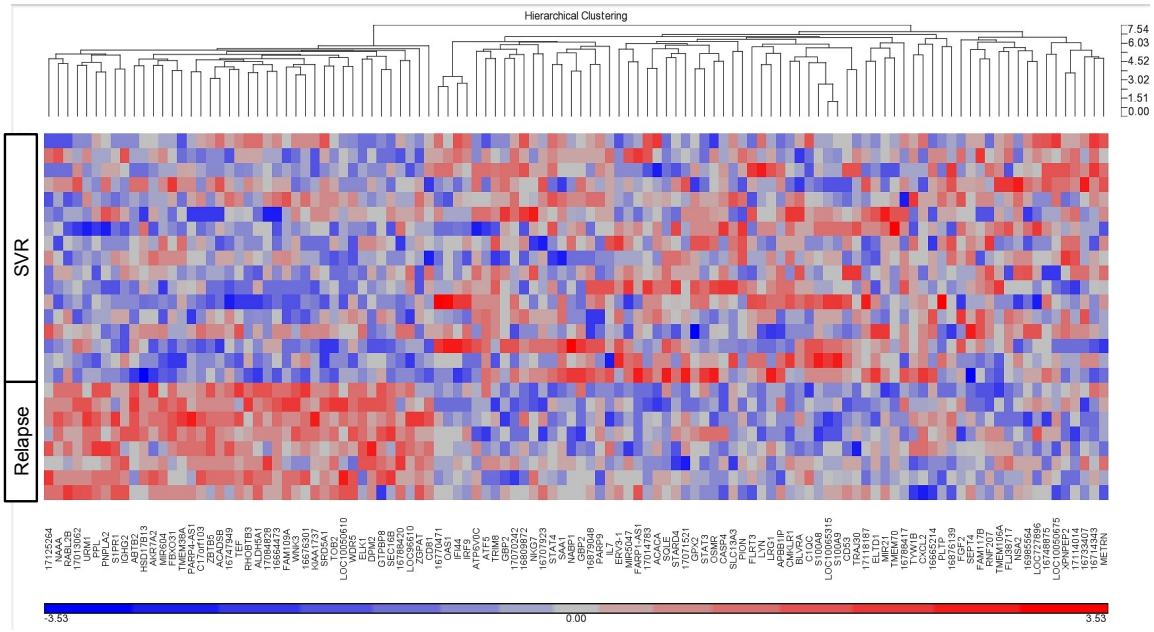
Supplementary Figure 2: Rapid down-regulation of endogenous interferon signaling in PBMC. Presented are top canonical pathways identified by IPA as changing over the course of treatment by day 6-11 (a) and by EOT at week 24 (b). Genes in the top 1% of the rank-order list were used for assessment. Ratios represent numbers of genes differentially expressed at the corresponding time points compared to pre-treatment that are assigned to specific pathways. Denominators indicate the numbers of genes annotated in the corresponding pathways. –Log (p-values) of 1.3 ($p = 0.05$) represent the cut-off for significance of these enrichments. Genes down-regulated at the indicated time-points compared to pre-treatment are shown in bold font.



Supplementary Figure 3: Expression of selected ISGs as measured by qRT-PCR in blood samples and displayed by treatment outcome. Expression does not differ by treatment outcome while on therapy; however, increases occurred during post-treatment relapse. Shown are individual values with group medians and interquartile range. P-values are for differences between SVR and relapse groups by Mann-Whitney test at the indicated time-points with correction for multiple testing. SVR in black, relapse in red. Number of patients tested (n) is indicated.



Supplementary Figure 4: Hepatic interferon and receptor expression levels in the patient who relapsed.
a) Total interferon expression decreases during treatment in the patient who relapsed. Relative gene expression of all measured interferons was summed at each time-point.
b) qRT-PCR for individual interferons was performed with 5-15 ng of RNA per reaction with technical duplicates. LLOD = lower limit of detection.
c) Relative expression ratios of individual interferons in pre-treatment and EOT liver biopsies, considering the sum of expression of all measured interferons as 100%, as described in the methods.
d) Treatment-induced changes in expression of interferon receptors.



Supplementary Figure 5: Heatmap of genes differentially expressed after SOF/RBV treatment in the unpaired EOT liver biopsies in patients who relapsed (n=8) vs. achieved SVR (n=17). The top 1% of differentially expressed genes were filtered using cutoffs of >1.2 for fold difference and unadjusted p-values of < 0.05. Microarray expression data was used to create a hierarchical clustering of samples using a Euclidean dissimilarity measure with average linkage. Red color indicates genes with higher relative expression with respect to treatment outcome.

Tables

Supplementary Table 1: Patient demographics for microarray expression analysis in paired liver biopsies

Patient ID[1]	Age (years)	Gender	Race[2]	HCV Genotype	Viral load (log_{10}, day 0)	Day of AST/ALT normalization	*IFNL4* Genotype[3]	*IFNL3* Genotype[4]	*IFNL3* Genotype[5]	Ribavirin Dose[6]	ISHAK Fibrosis (pre/EOT)[7]	HAI Inflammation (pre/EOT)[7]	Treatm Outcor
l6P1-2)	45	F	AA	1b	5.73	Day 3	ΔG/TT	CT	AC	High	1/1	6/2	SVR
l6P3-4)	58	F	AA	1a	6.51	Day 3	ΔG/ΔG	TT	AA	High	0/0	8/5	SVR
l6P5-6)	55	M	AA	1a	5.82	Day 3	TT/TT	CC	CC	High	0/0	5/2	SVR
l6P7-8)	61	F	AA	1a	7.03	Day 7	ΔG/TT	CT	AC	High	2/1	8/2	SVR
l6P15-16)	59	M	AA	1a	3.61	Day 7	ΔG/TT	CT	AC	High	1/1	5/3	SVR
l6P13-14)	55	M	AA	1a	6.54	Day 7	ΔG/TT	CT	AC	Low	2/2	6/1	Relap
l6P9-10)	51	F	AA	1a	5.76	Day 10	TT/TT	CC	CC	Low	1/2	10/7	SVR
l6P11-12)	30	F	HA	1b	5.05	Day 3	ΔG/TT	CT	CC	High	0/1	7/3	SVR

[1] GEO identification codes for microarray data available online is shown in the parentheses (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?token=uxwtaakqxncxxyj&acc=GSE51699)
[2] AA (African-American), HA (Hispanic-American)
[3] *IFNL4* genotype as determined by the rs368234815 variant (TT/ΔG)
[4] *IFNL3* genotype as determined by the rs12979860 variant (C/T)
[5] *IFNL3* genotype as determined by the rs4803217 variant (A/C)
[6] High ribavirin = weight-based 1000-1200 mg/day, low ribavirin = 600 mg/day
[7] ISHAK-fibrosis (0-6) and Histological Activity Index (HAI) (0-18) scores on pre- and EOT liver biopsies

Supplementary Table 2: Gene list identified by microarray gene expression analysis in paired liver biopsies; uploaded as separate excel file

Supplementary Table 3: Peripheral proteomic profiles of chemokines and cytokines during SOF/RBV therapy

		Pre-treatment	Day 6-11	Week 12	Week 24	Healthy Volunteer
Chemokines	IP-10	930 (560-1344)	**232 (176-355)**	**203 (148-236)**	**203 (162-287)**	230 (195-304)
	Mip-1B	221 (162-289)	**152 (112-202)**	180 (130-241)	**140 (109-206)**	288 (148-422)
	Eotaxin-3	12 (9-15)	11 (9-13)	12 (10-15)	10 (9-15)	19 (13-29)
	MCP4	975 (696-1507)	986 (764-1325)	**1174 (907-1504)**	1099 (896-1384)	1208 (925-1660)
	TARC	513 (385-830)	617 (445-989)	**702 (499-1204)**	**758 (520-1075)**	729 (508-1038)
	Eotaxin	481 (351-829)	**394 (293-616)**	532 (401-853)	489 (363-708)	892 (554-1291)
	MCP1	353 (223-625)	**332 (206-470)**	312 (222-612)	316 (253-517)	450 (414-857)
	MDC	3427 (2257-4136)	2676 (2158-3473)	3503 (2294-4234)	3341 (2639-3721)	3049 (2106-3529)
Cytokines	IL-10	6.7 (5.6-11.3)	ND	**5.4 (4.5-9.0)**	ND	4.8 (3.2-5.8)
	IFN-γ	2.1 (1.4-3.1)	ND	**1.5 (1.0-2.2)**	ND	1.2 (0.9-3.5)
	GM-CSF	1.4 (0.9-2.2)	ND	1.3 (0.9-2.5)	ND	0.8 (0.5-1.8)
	IL-2	0.7 (0.4-1.1)	ND	0.8 (0.4-1.5)	ND	0.3 (0.1-0.9)
	IL-12	3.2 (2.0-8.0)	ND	2.8 (1.9-7.0)	ND	2.2 (1.2-3.6)
	IL-1B	2.9 (2.4-3.6)	ND	3.0 (2.1-3.5)	ND	3.2 (2.5-4.5)
	IL-8	27 (19-47)	22 (17-38)	24 (20-55)	21 (15-42)	34.8 (0-86.8)
	IL-6	1.9 (0.9-3.3)	1.7 (1.2-2.2)	1.9 (1.0-3.1)	1.6 (1.0-2.5)	0.6 (0.5-1.4)
	TNF-α	16.7 (14.8-18.5)	18.1 (16.0-20.2)	16.6 (14.8-18.3)	18.1 (15.4-20.8)	19.8 (1.9-37.6)
	TGF-β1 (ng/ml)	15.4 (13.3-18.4)	16.3 (14.4-19.1)	15.1 (12.6-19.5)	15.0 (13.2-20.2)	14.8 (10.1-31.9)
	IFN-α2	UD	UD	UD	UD	UD
Fibrosis marker	TIMP1 (ng/ml)	233 (210-299)	233 (195-266)	249 (205-288)	242 (218-290)	214 (176-237)

Pre-treatment, day 6-11, week 12, and week 24 indicate the time samples were collected post-initiation of therapy, with week 24 representing the end of treatment (EOT). All values are pg/ml except for TIMP1 and TGFB1 (ng/ml). Shown are medians with interquartile ranges. Values significantly different from baseline are bolded as determined by the Wilcoxon matched-pairs signed rank test ($p<0.01$). N=44 patients (30 SVR, 14 relapse). Results from 5 healthy controls are shown for illustrative comparison but were not analyzed for statistical differences. UD = undetectable. ND= not done.

Supplementary Table 4: Gene list identified by microarray mRNA gene expression analysis in PBMC; uploaded as separate excel file

Supplementary Table 5: Patient demographics for EOT microarray mRNA expression analysis in unpaired liver biopsies

Patient ID[1]	Age (years)	Gender	Race[2]	*IFNL4* Genotype[3]	*IFNL3* Genotype[4]	*IFNL3* Genotype[5]	Ribaviriin Dose[6]	ISHAK Fibrosis Score[7]	HAI Inflammation Score[7]	Days after treatment of EOT biopsy[8]	Treatment Outcome	Days after treatment patient relapsed
11 (5143)	56	F	AA	ΔG/TT	CT	AC	High	0	3	14	SVR	N/A
12 (5142)	62	M	AA	ΔG/TT	CT	AC	High	1	5	7	SVR	N/A
13 (5145)	55	M	AA	ΔG/ΔG	TT	AA	High	0	2	2	SVR	N/A
14 (5149)	55	M	AA	ΔG/ΔG	TT	AA	High	6	12	2	SVR	N/A
15 (5150)	58	M	AA	ΔG/TT	CT	AC	High	0	1	38	SVR	N/A
16 (5147)	55	M	AA	ΔG/TT	CT	AC	High	2	2	2	SVR	N/A
17 (5144)	54	F	AA	ΔG/ΔG	TT	AA	High	1	9	2	SVR	N/A
18 (5151)	55	F	AA	ΔG/TT	CT	AC	High	2	7	10	SVR	N/A
19 (5146)	57	M	AA	TT/TT	CC	CC	High	0	3	1	SVR	N/A
20 (5148)	54	F	EA	TT/TT	CC	CC	High	0	3	2	SVR	N/A
21 (5158)	56	M	AA	TT/TT	CC	CC	Low	1	5	4	SVR	N/A
22 (5156)	53	F	AA	ΔG/TT	CT	AC	Low	1	3	5	SVR	N/A
23 (5155)	26	F	EA	ΔG/TT	CT	AC	Low	0	1	3	SVR	N/A
24 (5152)	75	F	EA	ΔG/TT	CT	AC	Low	4	3	6	SVR	N/A
25 (5153)	50	M	AA	ΔG/TT	CT	AC	Low	1	3	7	SVR	N/A
26 (5157)	57	M	AA	ΔG/TT	CT	AC	Low	1	3	2	SVR	N/A
27 (5154)	46	F	AA	ΔG/ΔG	CT	AC	Low	0	3	14	SVR	N/A
28 (5160)	55	M	EA	TT/TT	CC	CC	High	3	4	20	Relapse	57
29 (5159)	47	M	AA	ΔG/ΔG	TT	AA	High	0	6	5	Relapse	35
30 (5165)	59	M	AA	ΔG/ΔG	TT	AA	Low	0	3	2	Relapse	57
31 (5163)	43	F	AA	ΔG/ΔG	TT	AA	Low	0	2	1	Relapse	57
32 (5162)	65	M	AA	ΔG/TT	CT	AC	Low	2	2	2	Relapse	16
33 (5166)	58	M	AA	ΔG/ΔG	CT	AC	Low	2	7	2	Relapse	16
34 (5164)	52	F	AA	ΔG/TT	CT	AC	Low	1	3	2	Relapse	29
35 (5161)	55	M	AA	ΔG/TT	CC	CC	Low	2	7	3	Relapse	15

[1] GEO identification codes for microarray data available online is shown in the parentheses (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?token=uxwtaakqxncxxyj&acc=GSE51699)
[2] AA (African-American), EU (European-American)
[3] *IFNL4* genotype as determined by the the rs368234815 variant (TT/ΔG)
[4] *IFNL3* genotype as determined by the rs12979860 variant (C/T)
[5] *IFNL3* genotype as determined by the rs4803217 variant (A/C)
[6] High ribavirin = weight-based 1000-1200 mg/day, low ribavirin = 600 mg/day
[7] ISHAK-fibrosis (0-6) and Histological Activity Index (HAI) (0-18) scores from EOT liver biopsies
[8] Timing of liver biopsy in days after the end of treatment
N/A is not applicable

Supplementary Table 6: Gene list results for microarray mRNA gene expression analysis in EOT liver biopsies; uploaded as separate excel file