Data in Brief

Type I and type II interferon responses in two human liver cell lines (Huh-7 and HuH6)

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ABSTRACT

Most studies investigating the biology of Hepatitis C virus (HCV) have used the human hepatoma cell line Huh-7 or subclones thereof, as these are the most permissive cell lines for HCV infection and replication. Other cell lines also support replication of HCV, most notably the human hepatoblastoma cell line HuH6. HCV replication in cell culture is generally highly sensitive to interferons (IFNs) and differences in the IFN-mediated inhibition of virus replication may reflect alterations in the IFN-induced antiviral response inherent to different host cells. For example, HCV replication is highly sensitive to IFN-γ treatment in Huh-7, but not in HuH6 cells. In this study, we used microarray-based gene expression profiling to compare the response of Huh-7 and HuH6 cells to stimulation with IFN-α and IFN-γ. Furthermore, we determined whether the resistance of HCV replication in HuH6 cells can be linked to differences in the expression profile of IFN-regulated genes. Although both cell lines responded to IFNs with rapid changes in gene expression, thereby demonstrating functional type I and type II signaling pathways, differences were observed for a number of genes. Raw and normalized expression data have been deposited in GEO under accession number GSE68927.

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2. Experimental design, materials and methods

2.1. Cell culture experiments and RNA isolation

The hepatoma cell line Huh-7 is the most commonly used cell line to study the biology of the human pathogen Hepatitis C virus (HCV) [1]. In these cells, HCV replication is strongly inhibited by both interferon-α (IFN-α) [2] as well as interferon-γ (IFN-γ) [3]. In the hepatoblastoma cell line HuH6, however, HCV replication is largely resistant to treatment with IFN-γ but not IFN-α [4]. To analyze the IFN-γ and IFN-α response in Huh-7 and HuH6 cells, we decided to perform a microarray-based gene expression analysis. To this end, Huh-7 and HuH6 cells, that were grown in Dulbecco’s modified minimal essential medium (Life Technologies, Karlsruhe, Germany) supplemented with 10% fetal calf serum, 2 mM l-glutamine, nonessential amino acids, 100 μg of penicillin/mL, and 100 μg of streptomycin/mL at 37 °C and 5% CO2, were plated in 10-cm cell culture petri dishes at 80% cell confluence and treated with either 1000 IU/mL IFNα-2a (PBL Laboratories, Acris, Herford, Germany), 1000 IU/mL IFN-γ (Roche, Basel, Switzerland), or remained untreated for 24 h. Total RNA was extracted

1. Direct link to deposited data

http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE68927

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from these samples by a GITC-based protocol [5]. RNA integrity was confirmed by agarose gel electrophoresis and RNA concentration was determined by measurement of OD at 260 nm on a NanoDrop Lite (Thermo Scientific, Braunschweig, Germany).

2.2. Microarray experiments

For first-strand cDNA synthesis, 13.5 μg total RNA was incubated as published before [6] with polyadenylated control RNAs and T7-oligo (dT)24 primer [5'-GGCGAGTTAGTATGAGTACACTAGTATGAGTACACTACGAGCGG(dT)24-3'] at 70°C for 10 min and put on ice. Next, the first-strand buffer mix (4 μL of 5 x the first-strand buffer, 2 μL 0.1 M dithiothreitol (DTT), and 1 μL 10 mM dNTPs) was preincubated at 42°C for 2 min. After addition of 200 μL (2 units) Superscript II (Life Technologies, Karlsruhe, Germany), incubation was continued at 42°C for 1 h. For second-strand synthesis, 30 μL 5 x the second-strand buffer, 91 μL RNase-free water, 3 μL 10 mM dNTPs, 4 μL (40 U) Escherichia coli DNA polymerase I (Life Technologies), 1 μL (12 U) E. coli DNAligase (TaKaRa, Gennesvilliers, France), and 1 μL (2 U) RNase H (TaKaRa) were added, and the mix was incubated at 16°C for 2 h. Then 2.5 μL (10 U) T4 DNA polymerase I (TaKaRa) were added at 16°C for 5 min. The reaction was stopped by the addition of 10 μL 0.5 M EDTA, double-stranded (ds) cDNA was extracted with phenol/chloroform, and the aqueous phase was recovered by phase-lock gel separation (Eppendorf, Hamburg, Germany). After precipitation, the cDNA was restored in 12 μL RNase-free water. Five microliters ds cDNA were used to synthesize biotinylated cRNA using the BioArray High Yield RNA Transcript Labeling Kit (Enzo Diagnostics, NY). Labeled cRNA was purified using the RNeasy Mini Kit (Qiagen, Hilden, Germany). Fragmentation and hybridization of 10 μg cRNA to GeneChip HG-U133 Plus 2.0 microarrays (Affymetrix, Santa Clara, CA) for 16 h at 45°C, as well as washing and staining on a Fluidics Station 450 (Affymetrix), and scanning of the arrays in a GeneArray Scanner 2500 (Agilent, Palo Alto, CA) were performed according to the Affymetrix Gene Expression Analysis Technical Manual.

2.3. Signal processing and normalization

Raw Affymetrix data (.CEL-files) were further processed using the Chipster software, version 3.4.0 [7]. Signals were normalized within one cell line (three treatment groups per cell line: mock, IFN-α and IFN-γ) using the RMA method and expressed on a log2-transformed scale. Probe-sets were remapped to 19,674 Entrez Gene IDs using a custom CDF file (version 12, Thompson and Meng microarray lab, University of Michigan) [8] and expression calls (A: absent, M: moderate, or P: present) were calculated using the MAS5 algorithm. Without further processing and filtering, data for Huh-7 and HuH6 cells were merged and exported into an Excel file for user-friendly interactive filtering (Supplementary data file 1).

2.4. Analysis of IFN-induced genes

Albeit genes induced by IFN, termed IFN-stimulated genes (ISGs), have been defined and known for a long time (e.g. http://www.interferome.org [10]) [11–21], the exact set and number of genes that are regulated by IFN varies between different cell types and might substantially affect the cells’ capacity to interfere with the replication of specific viruses. We therefore compared the ISG profile of the two hepatocyte-derived cell lines Huh-7 and HuH6, which are widely employed for research on hepatitis viruses, especially Hepatitis C virus (HCV). For this analysis, we defined ISGs as (1) being called “present” in the IFN-treated sample and (2) being upregulated at least 1.5-fold (0.58 on a log2-scale) upon IFN-treatment. For IFN-α, we found 269 ISGs in Huh-7 and 109 ISGs in HuH6, with 81 being common to both (Fig. 1). For IFN-γ, we found 207 ISGs in Huh-7 and 202 in HuH6, with 112 genes in common to both cell lines (Fig. 1). The genes that were most strongly induced upon IFN-α treatment in both cell lines include well-known prototype ISGs, such as MX1, IFIT1 (IFG56), IFIT3, IFI6 and OAS1-3 (Table 1). For IFN-γ, too, well-established prototype ISGs were strongly upregulated, such as GBP1, GBP3 or TAP1 (Table 1).

2.5. ISGs differentially induced in Huh-7 versus HuH6

We then analyzed the induced ISG profiles of the two cell lines for differentially regulated genes, i.e. genes whose transcriptional regulation upon IFN-treatment is significantly different between Huh-7 and HuH6. For this analysis, we defined IFN-α or IFN-γ ISGs as being “present” and upregulated by at least 1.5-fold in either Huh-7 or HuH6 upon treatment with the respective IFN, resulting in 301 ISGs for IFN-α and 292 ISGs for IFN-γ (excluding Affymetrix controls, see Supplementary data file 1). To generate ISG profiles for Huh-7 and HuH6, ISGs were then ranked based on their fold-change within the respective cell line, with rank 1 being awarded to the gene with highest induction. Plotting the ranked profiles against each other allows for easy visual identification of the ISGs most strongly differing in their regulation between Huh-7 and HuH6 (Fig. 2). Surprisingly, for IFN-α, MX1, being one of the most strongly induced and best characterized ISGs, only ranks

Table 1

| Gene symbol | FC Huh-7 | Gene symbol | FC HuH6 | Gene symbol | FC Huh-7 | Gene symbol | FC HuH6 |
|-------------|---------|-------------|---------|-------------|---------|-------------|---------|
| MX1         | 7.35    | IFT1       | 8.4     | GBP1        | 8.46    | GBP1        | 6.55    |
| IFIT1       | 6.93    | CMPK2      | 7.3     | PSMB9       | 7.49    | PSMB9       | 6.04    |
| CMPK2       | 5.93    | IF27       | 6.91    | TAPI1       | 5.85    | UBE26L      | 6.01    |
| DDXG0       | 5.9    | IFI44L     | 6.25    | PSMB8       | 5.74    | GBP3        | 5.72    |
| IFI6        | 5.82    | IFIH1      | 5.99    | RARRE35     | 5.67    | TAPI1       | 5.37    |
| IFIH1       | 5.81    | DDXG0      | 5.62    | UBD         | 5.58    | TRIM22      | 5.21    |
| IFIT3       | 5.33    | OAS5       | 5.5     | GBP3        | 5.1     | NMI         | 4.97    |
| OAS15       | 5.21    | IFI6       | 5.56    | IFIT3       | 5.04    | RARRE35     | 4.75    |
| OAS1        | 5.17    | IFIT3      | 5.37    | EPS1T1      | 4.97    | ERAP2       | 4.75    |
| OAS3        | 4.92    | OAS1       | 5.11    | CXX110      | 4.62    | CMKP2       | 4.69    |
| HERC6       | 4.84    | IFI44      | 4.92    | DDXG0       | 4.29    | UBD         | 4.62    |
| EPS1T1      | 4.79    | IFIT3      | 4.47    | NNM         | 4.28    | SERING1     | 4.5     |
| IRF9        | 4.2     | UBE26L     | 4.4     | TRIM22      | 3.81    | IFIT3       | 4.45    |
| OAS2        | 4.13    | OAS2       | 4.37    | PARP14      | 3.78    | PSMB8       | 4.12    |
| IFIT27      | 4.11    | ISG15      | 4.05    | PARP16      | 3.87    | LEPOT1      | 3.4    |
| DIXS8       | 3.8     | DTX3L      | 3.86    | CXX19        | 3.74    | DTX3L       | 3.88    |
| DIXG6L      | 3.62    | DIXS8      | 3.89    | IFI9         | 3.67    | PARP14      | 3.53    |
| IFTM1       | 3.55    | HERC6      | 3.48    | LGALS3BP    | 3.59    | FAP9        | 3.47    |
| IFI44L      | 3.44    | IFI9       | 3.43    | IFI8         | 3.47    | BATF2       | 3.4     |
| LGALS3BP    | 3.42    | PARP9      | 3.42    | CXX111      | 3.44    | DDXG0       | 3.37    |
56th in HuH6 (rank 1 in Huh-7), whereas IFI44 is a top-ISG in HuH6 (rank 11) but hardly induced in Huh-7 (rank 277). Further, CXCL-type chemokines CXCL1 (Gro-α), CXCL2 (Gro-β) and CXCL10 (IP-10) are upregulated in Huh-7, whereas they are not induced in HuH6 (Fig. 2). For IFN-γ, the CXCL chemokines, in particular CXCL10 and 11, are again strongly upregulated in Huh-7 (ranking 10th and 20th, respectively) and only to a much lesser extend in HuH6 (ranking above 100). Further, the MHC genes HLA-A, B and C are strongly induced in Huh-7 but substantially less so in HuH6. Conversely, IFI27 (rank 12) and ERAP2 (rank 8) are prominent ISGs in HuH6 but not in Huh-7 (ranking above 100).

As a quantitative measure to score differentially induced ISGs, we calculated a weighted rank difference (WRD) for each gene. The WRD for each gene was calculated as the difference in rank between the two conditions (Huh-7 and HuH6), weighted by the fold-change. The genes with the highest WRD values are indicated in Fig. 2. Table 2 lists the ISGs differentially induced in Huh-7 versus HuH6. ISGs were defined as “present” and upregulated at least 1.5-fold (0.58 on a log2 scale) in either Huh-7 or HuH6 and sorted for their weighted rank difference (WRD). The highest WRD corresponds to the strongest difference in induction between Huh-7 and HuH6 (see text).
was defined as the difference in a gene’s rank between Huh-7 and HuH6, normalized to the gene’s mean rank: \( \text{WRD} = r_{\text{Huh-7}} - r_{\text{HuH6}} \) (with \( r \) being the rank in the respective cell line), and therefore \( 0 \leq \text{WRD} \leq 2 \). Normalization to the mean rank accounts for the increasing possible variation for lower ranks; simply put, a rank difference of 50 is less significant in case of a gene ranking 250th and 300th (WRD = 0.18) as compared to a gene ranking 1st and 51st (WRD = 1.92).

Table 2 lists the most significant (WRD > 1) differentially regulated ISGs between Huh-7 and HuH6 for IFN-α and IFN-γ in Huh-7 (full list of ISGs with WRDs in Supplementary data file 1).

3. Discussion

In this study, we describe the experimental details used to compare the IFN-induced changes in gene expression in the two human liver derived cell lines Huh-7 and HuH6. A large number of genes have been classified as ISGs in the past [11–21]. The ISG database http://www.interferome.org [10] currently lists 3185 type I IFN regulated human genes in total, however with substantial differences between different cell or tissue types. For non-immune cells lines, typically 200 to 400 genes are upregulated robustly by IFN [14–17,20], depending on the chosen cut-off. This is in good agreement with our findings for Huh-7 (IFN-α: 269; IFN-γ: 207 genes > 1.5-fold) and HuH6 (IFN-α: 109; IFN-γ: 202 genes > 1.5-fold). Moreover, the genes that were most strongly upregulated in both cell lines (see Table 1) comprise prominent ISGs in Huh-7 and HuH6 cells. The reason for this apparent lack of IFN-α-stimulated ISGs in HuH6 cells likely reflects the arbitrary cutoff of 1.5-fold upregulation used to identify ISGs. However, comparing the 269 ISGs from Huh-7 to the 269 most upregulated genes in HuH6 (disregarding the fold-change cutoff) it only marginally increases the overlap between the two cell lines from 88 genes (see Fig. 1) to 102 genes, with the remaining 167 being unique to Huh-7 or HuH6, respectively. This argues against the hypothesis that HuH6 has a similar ISG profile, but lower overall induction values. In fact, the most strongly induced ISGs exhibit comparable fold-increases in both cell lines (see Table 1). Furthermore, the ability of HuH6 cells to mount a functional antiviral response is not compromised in general, as these cells are capable to inhibit the replication of several viruses upon treatment with IFN-α [4]. In contrast to type I IFN, the number of genes induced upon IFN-γ treatment (by at least 1.5-fold) was similar in Huh-7 and HuH6 cells, and the overlap of induced genes was more substantial (see Fig. 1). Nonetheless, even for IFN-γ, roughly half of the ISGs were unique to the respective cell line, again highlighting the cell-type dependence of the induced ISG profile.

In order to specifically analyze differences between the ISG profiles of Huh-7 and HuH6, we used a ranked list approach, screening for those genes, whose rank differed most between the two cell lines. These differentially regulated genes represent highly interesting candidates for future studies on functional differences between the IFN response in Huh-7 and HuH6 cells. For example, it has been shown before, that the IFN-γ response in HuH6 – in contrast to Huh-7 – cells is not capable to efficiently inhibit the replication of HCV [4]. In fact, we could show that one of the genes identified as being differentially regulated by IFN-γ in the two cell lines, DDX56L (WRD = 1.07, see Table 2), functionally contributes to this resistance phenotype of HCV in IFN-γ treated HuH6 cells [22].

The underlying reasons for the observed profound differences in the ISG profiles between Huh-7 and HuH6 cells and previously observed differences between other cell types remain largely elusive [11–21]. Subtle differences in the expression of certain “master regulators”, e.g., transcription factors or secreted signaling molecules, such as cytokines, may drive the up- (or down-) regulation of whole sets of effector genes. In line with this hypothesis, in their study across six different virus species, Schoggins and colleagues identified as some of the most broadly active ISGs master regulators, such as IRF1 (impacting all six viral species), RIG-I, MDA5 and IRF7 [20,23]. In our data, one striking difference between the cell lines was the production of several CXCL-type chemokines in response to IFN-α and IFN-γ, which was observed in Huh-7 but not in HuH6 cells. Furthermore, also the cytokines IL-8 (WRD 1.34 in IFN-α) and IL-7 (WRD 1.15 in IFN-γ), as well as the negative regulatory factor IRF2 (WRD 0.98 in IFN-α, WRD 0.95 in IFN-γ) were differentially regulated between the two cell lines. It is unclear if and to what extent these signaling modulators contribute to the observed differences in ISG expression profiles, but the findings represent interesting starting points for further investigations and may direct future experimentation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.gd.2015.12.017.

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