Identification of transcriptional networks during liver regeneration

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Summary

The molecular analysis of mammalian cellular proliferation *in vivo* is limited in most organ systems by the low turnover and/or the asynchronous nature of cell cycle progression. A notable exception is the partial hepatectomy model, in which quiescent hepatocytes reenter the cell cycle and progress in a synchronous fashion. Here we have exploited this model to identify regulatory networks operative in the mammalian cell cycle. We performed microarray-based expression profiling on livers 0 to 40 hours posthepatectomy corresponding to G₀, G₁ and S phase. Differentially expressed genes were identified using the statistical analysis program PaGE, which was highly accurate, as confirmed by quantitative RT-PCR of randomly selected targets. A shift in the transcriptional program from genes involved in lipid and hormone biosynthesis in the quiescent liver to those contributing to cytoskeleton assembly and DNA synthesis in the proliferating liver was demonstrated by biological theme analysis. In a novel approach, we employed computational pathway analysis tools to identify specific regulatory networks operative at various stages of the cell cycle. This allowed us to identify a large cluster of genes controlling mitotic spindle assembly and checkpoint control at the 40h time point as regulated at the mRNA level *in vivo*. 
Introduction

The liver is one of few organs that retain the capacity to rapidly respond to changes in mass and/or function in both humans and animals. This property has significant implications for a variety of clinical situations including surgical removal of a portion of the liver, such as that which occurs following tumor resection or living-related liver transplantation and for recovery from fulminant liver failure. In contrast to the synchronous and extensive loss of liver mass that occurs in surgical contexts and acute liver failure, the majority of human liver diseases are characterized by repetitive inflammatory or toxic insults to the liver that are associated with loss of liver cells as the result of necrotic or apoptotic cell death. As a consequence of repetitive injury, proliferative signals to hepatocytes are associated with increased risk of hepatocellular carcinoma. However, the mechanisms that regulate both normal and pathologic proliferation are still poorly understood.

A widely used experimental model of hepatic growth is the partial hepatectomy model in rodents in which approximately 70% of the liver is removed and restoration of liver mass occurs within 10 to 14 days (1). Within 30 minutes of the surgery, cytokine and growth factor stimulation leads to the activation of preexisting transcription factors including NF-κB, Stat3, AP-1 and C/EBPβ and induction of a large number of genes responsible for stimulating normally quiescent hepatocytes and nonparenchymal liver cells to reenter the cell cycle and ultimately restore the liver mass (2-5). The genes that are either increased from basal levels of expression or are induced de novo encode proteins involved in maintaining homeostasis and stimulating cells to reenter the cell
cycle and proliferate. In a model proposed by Fausto, there appear to be at least two distinct phases of liver regeneration that are regulated via different mechanisms: a priming phase in which quiescent hepatocytes are induced to reenter the cell cycle as a result of TNF-\(\alpha\) and IL-6 stimulation, followed by a second phase in which hepatocytes respond to growth factors and progress through the G\(_1\) stage of the cell cycle (2). The priming phase in the rodent hepatectomy model in which immediate-early genes are activated corresponds to the first 4 hours posthepatectomy(6,7). The peak of DNA synthesis occurs approximately 40 hours after resection in the mouse and the period immediately preceding this is associated with the induction of cell cycle genes including cyclin D1, fox M1b, cyclin dependent kinases and the cyclin dependent kinase inhibitor, p21 (also known as CDKN1A) (8-12). Many of the individual genes involved in the priming phase of liver regeneration have been identified using mouse genetic models and more recently through the use of high-density oligonucleotide arrays(6,13-22). However, information regarding the pattern of gene expression in the periods following this immediate early priming phase is still limited. In addition, as a consequence of the complexity and robust nature of the transcriptional changes that occur in response to partial hepatectomy, there remains much to be learned regarding the integration of the products of these genes into the complex signaling and transcriptional hierarchies that result in this highly synchronized regenerative response. In this study, we utilized a cDNA microarray enriched for genes expressed in hepatocytes to profile changes in gene expression in mouse liver cDNA samples isolated 0, 2, 16, and 40h posthepatectomy (23,24). We selected these time points in order to detect differentially expressed genes
during the priming phase, mid-G₁ and peak of S phase in the mouse partial hepatectomy model (Figure 1A).

Previous microarray studies performed using models of liver regeneration have produced lists of temporally regulated genes but have failed to establish how these genes may form regulatory networks (6,18-20). Moreover, these studies have predominantly identified metabolic factors and other highly expressed genes that are easily detected through microarray analysis. In the present study we highlight novel approaches to the analysis of microarray data, focusing specifically on key time points during the hepatocyte cell cycle that have previously been overlooked. We leverage novel computational tools to identify themes and regulatory networks that govern hepatic proliferation in vivo. We demonstrate that this approach identifies even those genes whose expression levels are below the sensitivity limit of microarray analysis, including those encoding growth factors and DNA binding proteins. This paradigm will be generally applicable to other expression data sets of similar or higher complexity.
Methods

Preparation of samples.

12-16 week old C57BL6/SV129 mice were subjected to partial hepatectomy as described previously (22). Animals were sacrificed and RNA was prepared from the remaining liver lobes, taken from mice at 0, 2, 16 and 40 h post-hepatectomy, by homogenization in guanidine isothiocyanate and purification by cesium chloride ultracentrifugation(25). All RNA samples were analyzed using an Agilent Bioanalyzer Lab-On-A-Chip Nano 6000 chip to determine the integrity and concentration of the samples. Only samples passing this quality control step with a ratio of the 28S to 18S RNA of ≥ 2.0 were used for expression analysis.

Microarray expression profiling and data analysis. 20 μg of total RNA was indirectly labeled using amino-allyl dUTP and an anchored oligo (dT20) to prime reverse transcription. Flourescent label (Cy™Dye, Amersham Pharmacia Biotech Ltd, NJ) was coupled to the cDNA and hybridized to the PancChip version 5.0 13K cDNA microarray (26,27). For each array hybridization, labeled liver RNA from one of the four time points was hybridized with a common control RNA sample labeled with a different Cy dye. The common control RNA comprised equal quantities of a mixture of RNAs taken from both wild type and C/EBPβ−/− mutant mice (28) prepared from quiescent (0h), 2h, 16h, 24h, 30h, 40h and 48h posthepatectomy. This diverse pool of RNA ensured good expression coverage and was used to minimize the production of zero denominators in the calculation of expression ratios for the time course analysis.
Four biological replicates were used for each of the 0h, 2h, 16h and 40h time points. For each array hybridization a dye swap hybridization was performed, such that for each time point two of the biological replicates were hybridized as test (Cy5: Red) vs. common control (Cy3: Green) and the other two biological samples as common control (Cy5) vs. test (Cy3). The replicate dye-swap analysis reduced the impact of dye bias or other labeling artifacts on the ratio of gene expression at a given time point. The median intensities of each spot on the array were measured by an Agilent Scanner using the GenePix version 5 software, and the ratio of expression for each element on the array was calculated in terms of M (log₂(Red/Green)) and A ((log₂(Red) + log₂(Green))/2)). The data was normalized by the print tip lowess method using the SMA (Statistical Microarray Analysis) package in R (29). For statistical analysis, genes were identified as differentially expressed using the “Pattern from Gene Expression” package (PaGE version 5.0) as described previously (30). Two-class, unpaired data tests were also performed to specifically identify genes that were differentially expressed by more than 1.5 fold when comparing the different time points: 0h vs 2h, 0h vs. 16h, and 0h vs. 40h. In all cases a false discovery rate (FDR) of 0.2 was chosen to identify differentially expressed genes. The microarray data are available through the MIAME compliant database RAD (RNA abundance database)(31) at http://www.cbil.upenn.edu/RAD.

**Quantitative real-time reverse transcription PCR (QPCR).** Differential gene expression was confirmed using QPCR. Liver RNA (500 ng) was reverse transcribed at 42°C for one hour with 1 µg Oligo (dT) primer (Invitrogen) and Superscript II reverse transcriptase. PCR reaction mixes were assembled using the Brilliant® SYBR Green
QPCR Master Mix (Stratagene, CA). 10 µM primers, 1 µl cDNA and the included reference dye at a 1:200 dilution were prepared according to manufacturer’s instructions. Reactions were performed using the SYBR Green (with Dissociation Curve) program on the Mx4000™ Multiplex Quantitative PCR System (Stratagene, CA). Cycling parameters were 95°C for 10 minutes and then 40 cycles of 95°C (30 s), 58°C or 60°C (1 minute), and 72°C (30 s) followed by a melting curve analysis. All reactions were performed with 4 biological replicates and 3 technical replicates with reference dye normalization. The median cycle threshold (CT) value was used for analysis, and all CT values were normalized to expression of the housekeeping gene TBP (confirmed not to be differentially expressed with microarray expression analysis). Primer sequences are available upon request. The Students t-test was used to confirm that the QPCR was significant and matched the direction of the fold change predicted by the array. An unpaired t-test using the one-tailed probability table with a p-value significance cutoff of 0.05 was used for all genes tested.

Biological theme analysis. The software application Expression Analysis Systematic Explorer (EASE) was used to discover biologically relevant themes in the lists of genes identified as significantly differentially expressed at 2h, 16h, and 40h post hepatectomy (32). Briefly, EASE first maps Entrez GeneID identifiers for all genes assayed using the PancChip to gene categories represented by GO function. Within various categorical systems supported by GO function, the "Population Total" is determined for each system of gene categorization (e.g. Biological Process or Molecular Function), and the "Population Hits" are determined for every category within those systems (e.g. hormone...
metabolism or protein biosynthesis). In a second step, the lists of genes differentially expressed at each time point are analyzed to determine which functional categories are over-represented. Third, the probability of obtaining the number of genes in a certain pathway in the list of differentially expressed genes is then compared to the representation of the same pathway among all the genes on the microarray and is calculated as the Fisher exact probability. This probability is then used to calculate the metric known as the "EASE score", which is a conservative adjustment to the Fisher exact probability that weights significance in favor of themes supported by more genes and therefore yields more robust results. In order to be able to perform the EASE analysis, the 11,681 of the 13,008 EST clones on the PancChip M5.0 were annotated with Entrez Gene Identifiers (GeneIDs, formerly LocusIDs) using assembly annotation from the Database of Transcribed Sequences (DoTS version 9.0, 2004), and annotation tools available at the Database for Annotation, Visualization and Integrated Discovery (DAVID). The remaining EST clones were excluded from the analysis as they represented novel transcripts and these elements on the array could not be annotated with a GeneID. To prevent false over-representation of a particular GeneID, all duplicates were removed from the lists giving a population of 7125 unique GeneIDs, and 155, 259 and 479 unique GeneIDs representing genes differentially expressed by more than 1.5 fold at 2h, 16h and 40h respectively.

The data was analyzed for themes using Gene Ontology (GO) Cellular Compartment, Molecular Function and Biological Process provided by NCBI (33). The lists of up and down regulated genes at each time point were analyzed with the categorical overrepresentation function of EASE, and the most significantly
overrepresented categories were identified using EASE scores. All significant (p < 0.05) categories resulting from each list produced the overrepresented biological themes shown in Table 2S.

Pathway Analysis. Biologically relevant networks were drawn from the lists of genes that were differentially expressed at the 2h, 16h and 40h time points when compared to the 0h time point. This data was generated through the use of Ingenuity Pathways Analysis (IPA), a web-delivered application (www.Ingenuity.com) that enables the visualization and analysis of biologically relevant networks to discover, visualize and explore therapeutically relevant networks.

Expression data sets containing gene identifiers (Entrez Gene ID) and their corresponding expression values as fold changes were uploaded as a tab-delimited text file. Each gene identifier was mapped to its corresponding gene object in the Ingenuity Pathways Knowledge Base. The genes identified as differentially expressed by statistical analysis using PaGE described above, and which had a fold change between any of the time points of greater than 1.5 were included in the analysis. These genes, called Focus Genes, were then used as the starting point for generating biological networks. To start building networks, the application program queries the Ingenuity Pathways Knowledge Base for interactions between Focus Genes and all other gene objects stored in the knowledge base, and generates a set of networks. The program then computes a score for each network according to the fit of the network to the set of focus genes. The score indicates the likelihood of the Focus Genes in a given network being found together due to random chance. A score of greater than 2 indicates that there is a less than 1 in 100
chance that the Focus Genes were assembled randomly into a network due to random chance.
Results and Discussion

Identification of temporally regulated genes during liver growth

In order to identify genes that were differentially expressed at specific phases of the regenerative process, liver RNA samples were obtained from mice 0h, 2h, 16h and 40h after partial hepatectomy. These time points correspond to quiescent liver, early G₁, mid-G₁ and S phase of the hepatocyte cell cycle in this system (Figure 1A). One significant challenge inherent to high-throughput analysis of large scale changes in gene expression is the development of statistical methods that will maximize both the sensitivity and specificity of detection of differentially expressed genes. The PaGE statistical analysis package is a tool for analyzing microarray gene expression data useful for identifying expressed genes between two conditions, and for generating patterns across multiple conditions (30). PaGE uses an algorithm that generates discrete patterns using a false discovery rate (FDR) based on confidence measures. In the present study, we used a FDR of 20% to maximize sensitivity without significantly impacting accuracy. To identify candidate genes involved in early growth as well as later phases of liver regeneration, we also determined which genes were differentially expressed between time points. Two class, unpaired tests were performed to identify genes that were differentially expressed by more than 1.5 fold at 2, 16 and 40 hours posthepatectomy compared to quiescent liver.

Using these criteria, a total of 641 genes were found to be differentially expressed (Table 1A and Figure 1B). A sequential increase in the number of genes differentially expressed was observed with time after partial hepatectomy, with the comparison between 0h and 40h producing the largest change in gene expression. Table 1B lists the top 10 genes by
fold change up or down, for each of the comparisons made, while the complete list of affected genes is given in Table 1S (supplementary data). The groups of differentially expressed genes are shown schematically in the Venn diagram of Figure 1B, again highlighting the fact that the largest number of genes were differentially regulated at 40h posthepatectomy vs. 0h.

**Statistical analysis using PaGE is highly predictive of true differences in gene expression**

QPCR was used to determine how accurately the PaGE statistical analysis identified differentially expressed genes. 28 genes were chosen randomly from the 0h vs. 40h comparison. Of these 28 genes, 23 (82%) were found to be differentially expressed between 0h and 40h post hepatectomy by QPCR (Figure 2). Thus, PaGE is a highly accurate tool for the analysis of microarray data. The predictive power of the PaGE statistical analysis program was further highlighted by the correspondence between the preset 20% percent false discovery rate and the fact that about 20% of the genes showed no statistically significant change in gene expression by QPCR.

**Identification of global programs important for homeostatic and proliferative responses in the proliferating liver.**

Coordinated changes in expression of networks of genes involved in growth or homeostatic functions are essential for restoration of liver mass and survival during the posthepatectomy period. The Expression Analysis Systematic Explorer (EASE) program (see description in Methods) was used to identify important biological themes
overrepresented among genes that were differentially expressed at 2h, 16h and 40h posthepatectomy(32). Figure 3 summarizes some of the most significant themes that were identified using this analysis while a complete list of themes with significant scores is contained within Table 2S.

Genes involved in steroid and lipid metabolism were down-regulated as early as the 2h posthepatectomy time point and remained decreased throughout the remainder of the time course examined (Figure 3A). At the 16h posthepatectomy time point, which corresponds to hepatocyte mid-G1 phase, genes involved in nucleotide and protein synthesis as well as cytoskeletal organization were upregulated and remained upregulated 40h posthepatectomy. At 40h post-surgery, when the peak of S-phase is reached, several additional biological themes focused on nucleotide metabolism were overrepresented, likely corresponding to the increased need of the hepatocytes during DNA replication. Taken together, the results of the EASE analysis demonstrate a shift to those transcriptional programs that encode proteins involved in DNA synthesis and mitosis with a corresponding reduction in the expression of genes encoding proteins involved in most metabolic functions, which is summarized in the scheme shown in Figure 3B.

**Identification of biologically relevant networks.** Although the EASE analysis provided information regarding changes in large categories of biological processes, we were also interested to understand how individual genes were integrated into specific regulatory and signaling networks. This type of analysis has not been reported in microarray studies of the regenerating liver, and revealed several findings that have not been described previously for the partial hepatectomy model. Biologically relevant networks were
drawn from the lists of genes that were differentially expressed at the 2h, 16h and 40h time points through the use of Ingenuity Pathways Analysis (IPA) (see Methods for details). For each time point several major pathways were identified, and here we show the most significant network for each stage of liver regeneration analyzed. At 2h posthepatectomy, the pathway shown in Figure 4 was identified as being the most significant, containing 28 focus genes, with a highly significant score of 48. This pathway highlights a very powerful feature of this explorative tool. Our initial PaGE and EASE analysis reported above revealed that many genes involved in metabolism were differentially expressed 2h posthepatectomy (Figure 3/Table 1B). However, many of the known growth response genes that are induced in early G₁ phase were not detected as part of our initial array analysis. All of these growth response genes are contained on the PancChip M5.0, but were not detected because of the sensitivity limit of this and other microarray platforms. As shown in Figure 4A the pathway analysis identified Fos, JunB, JunD and Myc as likely participants in early growth responses based on the differential expression of other genes in the same pathway. Prompted by this result, we then utilized the more sensitive QPCR analysis to show that Fos, JunB, JunD and Myc were upregulated 209, 29, 22 and 14 fold respectively. The inclusion of these QPCR data confirmed the results of previous studies demonstrating the induction of these proto-oncogenes in the partial hepatectomy model and allowed us to identify a link between Myc and DUSP6 (MKP3), an inhibitor of ERK/MAP kinase signaling activity(34). To our knowledge, this is the first report of MKP3 expression and upregulation posthepatectomy in the liver.
At 16h posthepatectomy, the network shown in Figure 5 contained 35 focus genes, with a highly significant score of 61. The inclusion of the QPCR expression value for Myc at this time point identified regulatory links to other genes that were differentially expressed at the 16h posthepatectomy time point. The Myc targets that were differentially expressed encode proteins involved in diverse processes including cytokine signaling (ARTS-1)(35,36), matrix remodeling (SPARC)(37) and cell cycle progression (p21)(12).

The 40h time point corresponds to the peak of hepatocyte S phase in the partial hepatectomy model. Analysis of genes differentially expressed at this point identified several regulatory networks including pathways involved in DNA replication (TOP2A(38), RPA1(39), PCNA(40)), mitotic spindle assembly (MAPRE(41), DCTN2(42), CDC2(43), RACGAP1(44,45)) and mitotic checkpoint control (YWHAQ(46), MAD2L1(47), AURKB(48), CKS1B(49), BIRC5(50), NPM1(51)) (Figure 6). Our findings underscore the requirement for coordinate regulation of cytoskeletal and chromosomal components of mitotic complexes prior to the G2/M phase transition (52).

(53). We demonstrate here that mRNA levels for a large number of genes important for G2/M phase progression at the S phase peak are regulated coordinately, strongly supporting the notion that either transcriptional activation and/or posttranscriptional stability play a key role in phases of cell cycle progression beyond the G1 phase. While our analysis measures steady state levels of mRNA and therefore does not distinguish between these two mechanisms, several genes identified on our array including Mad2L1, Bub1b and Cdc2 are E2F transcriptional targets, suggesting that
similar to other growth models, E2Fs may be responsible for the upregulation of these mitotic checkpoint genes in the regenerating liver (54,55). Our ability to detect small changes in gene expression at the 40h posthepatectomy time point is likely to be a function of the highly synchronous nature of this in vivo model of cell cycle progression, a characteristic unique to the hepatectomy model.

Conclusion
In this study, we examined the changes in gene expression that occur following partial hepatectomy at selected time points with the aim of understanding the biological processes and specific regulatory networks that are important during early priming stages of the regenerative process and later time points corresponding to mid-G1 and S phase. Through the use of a variety of computational analysis tools, we have identified genes that are differentially expressed during various stages of liver regeneration and characterized biological processes and regulatory networks that provide both global and specific information regarding this highly synchronized proliferative and homeostatic response. While the links between individual genes identified by Ingenuity pathway analysis are derived from the scientific literature, to our knowledge, this is the first description of the relevance of many of these regulatory networks in the partial hepatectomy model. In addition, we demonstrate that the use of pathway analysis helps to overcome two problems of microarray expression profiling, that is both its limited sensitivity and the absence of certain genes on a given array platform. Finally, although transcriptional regulation is a key process by which protein function is regulated, pathway analysis can also include genes in a regulatory network that are modified
posttranslationally or as a result of protein-protein interactions that may also be important regulatory mechanisms. The approaches taken here for the analysis of the liver regeneration paradigm can serve as a model for the dissection of many other complex biological processes.
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Table 1A. PaGE Analysis of significantly differentially expressed genes between time points: two Class, unpaired data analysis with 20% FDR.

| Comparison   | Total | Up regulated (>1.5) | Down regulated (<-1.5) |
|--------------|-------|---------------------|------------------------|
| 0h to 2h     | 281   | 106                 | 49                     |
| 0h to 16h    | 489   | 127                 | 132                    |
| 0h to 40h    | 1155  | 386                 | 93                     |

Table 1B. Top 10 up or down regulated genes identified in each of the comparisons shown in Table 1A.

| Top 10 upregulated genes | Top 10 downregulated genes |
|--------------------------|-----------------------------|
| Entrez GeneID | Gene symbol | Fold change | Entrez GeneID | Gene symbol | Fold change |
| 0 h vs. 2 h comparison |
| 16006 Igfbp1 | 32.6 | 14870 Gstp1 | -6.2 |
| 100620 AK033727 | 14.2 | 14869 Gstp2 | -5.5 |
| 229751 LOC229751 | 11.9 | 15495 Hsd3b4 | -4.3 |
| 17750 Mt2 | 9.2 | 20341 Selenbp1 | -3.1 |
| 14262 Fmo3 | 8.8 | 13107 Cyp2f2 | -2.8 |
| 56031 Ppie | 8.5 | 105171 Arrdc3 | -2.7 |
| 12227 Btg2 | 7.8 | 17836 Mug1 | -2.7 |
| 22072 Prss2 | 7.3 | 246277 Csad | -2.6 |
| 11723 Amy2 | 7.1 | 103781 AK033431 | -2.5 |
| 69060 Php1 | 7.1 | 15492 Hsd3b1 | -2.4 |
| 0 h vs. 16 h comparison |
| 16819 Lcn2 | 120.7 | 12350 Car3 | -21.0 |
| 20209 Saa2 | 67.3 | 15495 Hsd3b4 | -9.0 |
| 11808 Apoa4 | 23.6 | 12401 Serpina6 | -8.1 |
| 19014 Pparbp | 18.1 | 14859 Gsta3 | -5.8 |
| 234199 Fgl1 | 12.5 | 18478 Pah | -5.6 |
| 22151 Tubb2 | 7.9 | 66234 Sc4mol | -5.0 |
| 16006 Igfbp1 | 4.7 | 11522 Adh1 | -4.5 |
| 11520 Adfp | 4.6 | 110196 Fdps | -4.3 |
| 16426 Itlh3 | 3.6 | 13107 Cyp2f2 | -4.2 |
| 73710 2410129E14Rik | 3.4 | 107869 Cth | -3.9 |
| 0 h vs. 40 h comparison |
| 20209 Saa2 | 83.4 | 12350 Car3 | -15.5 |
| 16819 Lcn2 | 49.6 | 13107 Cyp2f2 | -6.9 |
| 11808 Apoa4 | 21.3 | 76971 2810007J24Rik | -5.6 |
| 22072 Prss2 | 14.0 | 15495 Hsd3b4 | -4.5 |
| 16592 Fabp5 | 9.9 | 17836 Mug1 | -4.0 |
| 66473 Ctrb | 9.6 | 12633 Cflar | -3.7 |
| 19014 Pparbp | 9.2 | 14081 Acs1 | -3.6 |
| 234199 Fgl1 | 8.8 | 231691 Sds | -3.6 |
| 8.4 IMAGE=5648967 | 20341 Selenbp1 | -3.4 |
| 22074 Try4 | 7.7 | 18703 Pigr | -3.3 |
Figure Legends

Figure 1. A. Phases of the hepatocyte cell cycle in the partial hepatectomy model. B. Venn diagram showing the number of temporally differentially regulated genes with expression changes greater than 1.5 fold up or down.

Figure 2. PaGE is an accurate statistical test for the identification of differentially expressed genes. Quantitative real-time PCR (QPCR) was used to confirm the results of the PaGE statistical analysis of the microarray data from the 0h vs. 40h comparison. The fold change values (log₂) of 28 genes randomly picked for verification are shown above. A Students t-test was performed on each of the QPCR results. Where significant, the p value is indicated by * p<0.05, ** p<0.01 and *** p<0.001. The p values of measurements that were insignificant with the QPCR t-test are shown below the name of the gene tested. As predicted by PaGE, 23 (82%) genes were found to be differentially expressed between 0h and 40h posthepatectomy.

Figures 3. Biological themes overrepresented at various time-points during liver regeneration after partial hepatectomy. A. Partial list of biological themes found to be overrepresented at a given time point posthepatectomy. The biological pathways indicated were identified using EASE and are listed with the corresponding p-values. A complete list of all statistically significant themes is contained in Table 2S (supplementary data). B. Schema summarizing important changes in gene expression of major biological processes during liver regeneration.
Figures 4. Ingenuity Pathway Analysis identifies a network of genes regulated during early G₁ phase in the liver in vivo. The network is displayed graphically as nodes (genes/gene products) and edges (the biological relationships between the nodes). The intensity of the node color indicates the degree of up- (red) or down- (green) regulation. As described in the Legend provided, nodes are displayed using various shapes that represent the functional class of the gene product. Edges are displayed with various labels that describe the nature of the relationship between the nodes (A, activation; B, binding; E, expression; I, inhibition; P, phosphorylation; T, transcription). Edges without a label represent binding only. The four nodes MYC, JUNB, JUND and FOS were identified by the pathway analysis as part of the network and their differential gene expression was determined subsequent to the pathway analysis by QPCR. A total of 28 differentially expressed "focus" genes were brought into this network with a highly significant score of 48. Uncommon gene symbols: DDX5, dead-box polypeptide; CANX, calnexin; H3F3B, histone H3B; PCK1, phosphoenolpyruvate carboxykinase; CEBPB, CCAAT/enhancer binding protein beta.

Figures 5. Ingenuity Pathway Analysis identifies a network of genes regulated during mid- G₁ phase in the liver in vivo. The network is displayed graphically as nodes (genes/gene products) and edges (the biological relationships between the nodes). For the explanation of the symbols and letters see legend to Figure 4. A total of 35 differentially expressed "focus" genes were brought into this network with a highly significant score of 61. Uncommon gene symbols: PCK1, phosphoenolpyruvate
carboxykinase; CDKN1A, p21; EP300, E1A binding protein p300; HSPCA, heat shock protein 1, alpha.

**Figures 6. Ingenuity Pathway Analysis identifies networks of genes regulated during S phase in the liver in vivo.** The network is displayed graphically as nodes (genes/gene products) and edges (the biological relationships between the nodes). For the explanation of the symbols and letters see legend to Figure 4. The above network was produced by combining the two highest scoring networks with a total of 31 differentially expressed "focus" genes and a highly significant score of 58. Uncommon gene symbols: AURKB, aurora kinase B; BIRC5, surviving; CCNE1, cyclin E1; CCNE2, cyclin E2; CDKN1A, p21; CDKN1B, p27Kip1; CDKN1C, P57KIP2; CEBPB, CCAAT/enhancer binding protein beta; DCTN1, dynactin 1; DCTN2, dynactin 2; DDIT3, GADD153; TFDP1, DP1; YWHAQ, 14-3-3 homolog.
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### Table A

| Comparison  | Category                                      | EASE Score |
|-------------|-----------------------------------------------|------------|
| 2 h DOWN    | hormone metabolism                            | 2.4E-03    |
|             | steroid biosynthesis                           | 9.1E-03    |
|             | lipid metabolism                               | 9.7E-03    |
|             | fatty acid metabolism                          | 1.3E-02    |
| 16h UP      | protein biosynthesis                           | 3.7E-09    |
|             | ribosome biogenesis and assembly                | 3.3E-06    |
|             | cytoskeleton organization and biogenesis       | 2.6E-04    |
|             | actin cytoskeleton                              | 2.6E-03    |
|             | microtubule cytoskeleton                       | 1.2E-02    |
|             | intermediate filament cytoskeleton             | 4.9E-02    |
| 16h DOWN    | hormone biosynthesis                           | 1.9E-02    |
|             | steroid biosynthesis                           | 3.3E-06    |
|             | lipid metabolism                               | 3.6E-06    |
|             | fatty acid metabolism                          | 3.1E-03    |
|             | amino acid and derivative metabolism           | 2.1E-05    |
| 40 h UP     | protein biosynthesis                           | 3.2E-12    |
|             | ribosome biogenesis and assembly                | 2.5E-07    |
|             | ribosome biogenesis                            | 1.6E-07    |
|             | purine nucleoside triphosphate biosynthesis    | 1.7E-02    |
|             | nucleoside triphosphate metabolism             | 1.7E-02    |
|             | cytoplasm organization and biogenesis          | 2.4E-07    |
|             | cytoskeleton organization and biogenesis       | 1.8E-03    |
|             | actin cytoskeleton                              | 1.1E-05    |
|             | intermediate filament cytoskeleton             | 3.4E-02    |
|             | microtubule                                    | 3.4E-02    |
| 40h DOWN    | hormone biosynthesis                           | 1.9E-02    |
|             | cholesterol metabolism                         | 2.4E-02    |
|             | steroid biosynthesis                           | 4.4E-05    |
|             | lipid metabolism                               | 3.2E-06    |
|             | fatty acid metabolism                          | 7.6E-05    |

### Diagram B

- **Steroid synthesis**
- **Protein synthesis**
- **Cytoskeleton**
- **DNA metabolism**

**Time Post Hepatectomy**

0 5 10 15 20 25 30 35 40
Supplementary Data Table 1S

List of genes that were differentially expressed during the partial hepatectomy time course with an absolute fold change of 1.5 or higher, as identified by PaGE analysis (as shown in Figure 1B). The list is ranked by category (based upon GO annotation from MGI) and within each category genes are listed in descending order by the maximal fold change observed across the time course. Only fold change values that were significant according to PaGE are shown. Clicking on the Entrez GeneID will take you to the appropriate entry for that gene at the NCBI website, providing detailed information and PubMed references. The complete dataset can be downloaded from the RNA Abundance Database (RAD) at http://www.cbil.upenn.edu/RAD/php/index.php.

| Entrez GeneID | Symbol    | Description                                           | Fold Differential Expression |
|--------------|-----------|-------------------------------------------------------|------------------------------|
|              |           |                                                      | 2 h  | 16 h | 40 h |
| **Apoptosis**|           |                                                      |     |      |      |
| 12227        | Btg2      | B-cell translocation gene 2, anti-proliferative       | 7.8  | 2.0  |      |
| 60599        | Trp53inp1 | transformation related protein 53 inducible nuclear protein 1 | 4.0  | 1.6  |      |
| 12633        | Cflar     | CASP8 and FADD-like apoptosis regulator                | -3.1 | -3.7 |      |
| 15370        | Nr4a1     | nuclear receptor subfamily 4, group A, member 1        | 2.2  |      |      |
| 20393        | Sgk       | serum/glucocorticoid regulated kinase                  | 2.2  | 1.5  |      |
| 171543       | Bmf       | Bcl2 modifying factor                                  | 2.1  |      |      |
| 12226        | Btg1      | B-cell translocation gene 1, anti-proliferative        | 1.8  | 1.3  |      |
| 11799        | Birc5     | baculoviral IAP repeat-containing 5                    | 1.6  |      |      |
| 110213       | Tegt      | testis enhanced gene transcript                        | -1.6 | -1.5 |      |
| 12048        | Bcl2l1    | Bcl2-like 1                                           | 1.5  |      |      |
| 17110        | Lzp-s     | P lysozyme structural                                  | 1.5  | 1.1  |      |
| **Biosynthesis**|         |                                                      |     |      |      |
| 107869       | Cth       | cystathionase (cystathionine gamma-lyase)              | -3.9 |      |      |
| 110639       | Prps2     | phosphoribosyl pyrophosphate synthetase 2             | 4.1  | 1.7  | 3.0  |
| 235293       | Sc5d      | sterol-C5-desaturase (fungal ERG3, delta-5-desaturase) homolog (S. cerevisae) | -1.7 | -3.4 | -2.2 |
| 14718        | Got1      | glutamate oxaloacetate transaminase 1, soluble         | 3.4  | 1.8  | 2.0  |
| 13121        | Cyp51     | cytochrome P450, family 51                            | -3.3 |      |      |
| 110391       | Qdpr      | quininoid dihydropteridine reductase                  | -2.2 | -1.4 |      |
| 15360        | Hmgcs2    | 3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2       | 2.1  |      |      |
| 234724       | Tat       | tyrosine aminotransferase                              | 2.3  | 1.2  |      |
| 11656        | Alas2     | aminolevulinic acid synthase 2, erythroid             | -2.2 | -1.6 | -1.9 |
| 18103        | Nme2      | expressed in non-metastatic cells 2, protein           | 1.6  | 2.0  |      |
| 69219        | Dda1      | dimethylarginine dimethylaminohydrolase 1             | -1.7 |      |      |
| 67307        | 3110049J23Rik | RIKEN cDNA 3110049J23 gene                           | -1.8 | -1.9 |      |
| 18263        | Odc1      | ornithine decarboxylase, structural 1                 | 1.7  | 1.8  |      |
| 14854        | Gss       | glutathione synthetase                                 | 1.6  |      |      |
| 27973        | Vkorc1    | vitamin K epoxide reductase complex, subunit 1        | -1.5 | -1.5 |      |
| 11984        | Atp6v0c   | ATPase, H+ transporting, V0 subunit C                 | 1.5  |      |      |
## Catabolism

| Gene ID | Gene | Description | 
|---------|------|-------------|
| 18478   | Pah  | phenylalanine hydroxylase | -5.6 -1.8 |
| 246277  | Csad | cysteine sulfenic acid decarboxylase | -2.6 -2.0 -1.9 |
| 11992   | Auh  | AU RNA binding protein/enoyl-coenzyme A hydratase | -1.6 -2.6 -1.4 |
| 212503  | Paox | polyamine oxidase | -1.9 |
| 12583   | Cdo1 | cysteine dioxygenase 1, cytosolic | 1.3 -1.7 |
| 14085   | Fah  | fumarylacetoacetate hydrolase | -2.1 |
| 13850   | Ephx2| epoxide hydrolase 2, cytoplasmic | -1.5 1.3 -1.6 |
| 20229   | Sat1 | spermidine/spermine N1-acetyl transferase 1 | 1.9 1.7 |
| 26443   | Psma6| proteasome (prosome, macropain) subunit, alpha type 6 | 1.6 |
| 19173   | Psmb5| proteasome (prosome, macropain) subunit, beta type 5 | 1.6 |
| 15233   | Hgd  | homogentisate 1, 2-dioxygenase | -1.5 |

## Catalytic activity

| Gene ID | Gene | Description | 
|---------|------|-------------|
| 66473   | Ctrb1| chymotrypsinogen B1 | 6.4 9.6 |
| 56031   | Ppie | peptidylprolyl isomerase E (cyclophilin E) | 8.5 2.1 2.2 |
| 114228  | Trygn16| trypsinogen 16 | 4.8 7.7 |
| 107568  | Wwp1 | WW domain containing E3 ubiquitin protein ligase 1 | 4.8 7.0 |
| 71665   | Fuca1| fucosidase, alpha-L-1, tissue | 5.2 |
| 70790   | 4432411E13Rik| RIKEN cDNA 4432411E13 gene | 5.8 4.1 |
| 14870   | Gstp1| glutathione S-transferase, pi 1 | -6.2 |
| 14859   | Gsta3| glutathione S-transferase, alpha 3 | -5.8 -2.0 |
| 76971   | 2810007J24Rik| RIKEN cDNA 2810007J24 gene | -1.8 -2.9 -5.6 |
| 13706   | Ela2 | elastase 2 | 4.3 |
| 67868   | Ela3b| elastase 3B, pancreatic | 3.4 3.9 |
| 67373   | 2210010C04Rik| RIKEN cDNA 2210010C04 gene | 3.4 3.6 |
| 110196  | Fdps | farnesyl diphosphate synthetase | -4.3 -2.5 |
| 22074   | Try4 | trypsin 4 | 3.6 1.6 7.7 |
| 109901  | Ela1 | elastase 1, pancreatic | 4.0 |
| 16426   | Itih3| inter-alpha trypsin inhibitor, heavy chain 3 | 3.6 3.2 |
| 67603   | Dusp6| dual specificity phosphatase 6 | 3.4 1.7 |
| 109697  | Cpa1 | carboxypeptidase A1 | 1.6 |
| 223775  | Pim3 | proviral integration site 3 | 2.1 |
| 12494   | Cd38 | CD38 antigen | 3.3 2.6 |
| 105349  | Akr1c18| aldo-keto reductase family 1, member C18 | -2.8 |
| 209186  | C730036D15Rik| RIKEN cDNA C730036D15 gene | 1.8 1.8 2.9 |
| 109660  | Ctrl | chymotrypsin-like | 2.2 1.8 |
| 16828   | Ldh1 | lactate dehydrogenase 1, A chain | 2.6 2.2 |
| 20322   | Sdh1 | sorbitol dehydrogenase 1 | -2.0 -2.8 -1.6 |
| 13430   | Dnm2 | dynamin 2 | 2.6 1.5 2.7 |
| 102022  | 9130231C15Rik| RIKEN cDNA 9130231C15 gene | -1.6 -2.2 -2.6 |
| 16612   | Klk6 | kallikrein 6 | 2.2 2.5 |
| 59044   | Rnf130| ring finger protein 130 | 1.8 1.4 |
| 15473   | Hrsp12| heat-responsive protein 12 | -1.8 -1.8 |
| 68652   | Map3k7ip2| mitogen-activated protein kinase kinase kinase 7 interacting protein 2 | 2.4 |
| Gene ID  | Gene Name          | Function/Annotation                                                                 |
|----------|--------------------|-------------------------------------------------------------------------------------|
| 76703    | Cpb1               | carboxypeptidase B1 (tissue)                                                        |
| 231842   | 6530401C20Rik      | RIKEN cDNA 6530401C20 gene                                                          |
| 74143    | Opa1               | optic atrophy 1 homolog (human)                                                     |
| 71207    | Nudt4              | nudix (nucleoside diphosphate linked moiety X)-type motif 4                          |
| 56734    | Tulp2              | tubby-like protein 2                                                                |
| 67931    | Serpinii2          | serine (or cysteine) proteinase inhibitor, clade I member 1                          |
| 53315    | Sult1d1            | sulfotransferase family 1D, member 1                                                |
| 226105   | Cyp2c70            | cytochrome P450, family 2, subfamily c, polypeptide 70                               |
| 212442   | Lactb2             | lactamase, beta 2                                                                   |
| 14651    | Hagh               | hydroxyacyl glutathione hydrolase                                                    |
| 75221    | Dpp3               | dipeptidylpeptidase 3                                                               |
| 66597    | Trim13             | tripartite motif protein 13                                                          |
| 13988    | Gck                | glucokinase                                                                         |
| 20768    | Sephs2             | selenophosphate synthetase 2                                                         |
| 11886    | Asah1              | N-acylsphingosine amidohydrolase                                                     |
| 13806    | Eno1               | enolase 1, alpha non-neuron                                                          |
| 19255    | Ptnp2              | protein tyrosine phosphatase, non-receptor type 2                                    |
| 229905   | BC037135           | cDNA sequence BC037135                                                              |
| 66887    | 1300002A08Rik      | RIKEN cDNA 1300002A08 gene                                                           |
| 98711    | Rdh10              | retinol dehydrogenase 10 (all-trans)                                                |
| 102294   | Cyp4v3             | cytochrome P450, family 4, subfamily v, polypeptide 3                                |
| 66120    | Fkbp11             | FK506 binding protein 11                                                             |
| 211770   | Trib1              | tribbles homolog 1 (Drosophila)                                                      |
| 69786    | 1810034M08Rik      | RIKEN cDNA 1810034M08 gene                                                           |
| 14711    | Gnm1               | glycine N-methyltransferase                                                          |
| 57028    | Pdxp               | pyridoxal (pyridoxine, vitamin B6) phosphatase                                        |
| 83814    | Nedd4l             | neural precursor cell expressed, developmentally down-regulated gene 4-like          |
| 69590    | 2310016C16Rik      | RIKEN cDNA 2310016C16 gene                                                           |
| 17449    | Mdh1               | malate dehydrogenase 1, NAD (soluble)                                               |
| 19141    | Lgmn               | legumain                                                                            |
| 268373   | Ppia               | peptidylprolyl isomerase A                                                           |
| 13039    | Ctsl               | cathepsin L                                                                         |
| 225326   | Pik3c3             | phosphoinositide-3-kinase, class 3                                                   |
| 16784    | Lamp2              | lysosomal membrane glycoprotein 2                                                    |
| 14858    | Gsta2              | glutathione S-transferase, alpha 2 (Yc2)                                             |
| 11674    | Aldoa              | aldolase 1, A isoform                                                                |
| 53381    | Prdx4              | peroxiredoxin 4                                                                     |
| 14228    | Fkbp4              | FK506 binding protein 4                                                              |
| 27361    | Sepx1              | selenoprotein X 1                                                                    |

**Cell cycle**

| Gene ID  | Gene Name                    | Function/Annotation                        |
|----------|------------------------------|--------------------------------------------|
| 16006    | Igfbp1                       | insulin-like growth factor binding protein 1|
| 14453    | Gas2                         | growth arrest specific 2                   |
| 21973    | Top2a                        | topoisomerase (DNA) II alpha                |

file:///C|/Table1S.htm (3 of 16)10/21/2004 7:37:40 AM
| Gene Symbol | Description                                      | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|-------------|--------------------------------------------------|---------------|---------------|---------------|
| 18538       | Pcna, proliferating cell nuclear antigen         | 3.5           |               |               |
| 12534       | Cdc2a, cell division cycle 2 homolog A (S. pombe)| 2.6           |               |               |
| 17242       | Mdk, midkine                                     | 2.2           |               |               |
| 12575       | Cdkn1a, cyclin-dependent kinase inhibitor 1A (P21)| 2.1, 2.0, 2.4 |               |               |
| 21761       | Morf4l1, mortality factor 4 like 1               | -1.9          |               |               |
| 12314       | Calm2, calmodulin 2                              | 1.2, 1.3, 2.3 |               |               |
| 19384       | Ran, member RAS oncogene family                  | 1.3           | 1.2           | 2.2           |
| 23872       | Ets2, E26 avian leukemia oncogene 2, 3' domain   | 2.1, 1.2, 1.4 |               |               |
| 29811       | Ndr2, N-myc downstream regulated gene 2          | -2.1, -1.5    |               |               |
| 20877       | Aurkb, aurora kinase B                           | 2.0           |               |               |
| 68275       | Rpa1, replication protein A1                     | 1.7           |               |               |
| 12315       | Calm3, calmodulin 3                              | 1.9           |               |               |
| 13713       | Elk3, ELK3, member of ETS oncogene family        | 1.9, 1.5      |               |               |
| 19387       | Rangap1, RAN GTPase activating protein 1          | 1.6           |               |               |
| 56150       | Mad2l1, nuclear factor of kappa light chain gene | 1.8, 1.8, 1.2 |               |               |
| 18035       | Nkbia, nuclear factor of kappa light chain gene  | 1.8, 1.8, 1.2 |               |               |
| 12313       | Calm1, calmodulin 1                              | 1.6, 1.7      |               |               |
| 13401       | Dmwd, dystrophia myotonica-containing WD repeat  | -1.6          |               |               |
| 54124       | Cks1, CDC28 protein kinase 1                     | 1.7           |               |               |
| 56397       | Morf4l2, mortality factor 4 like 2               | 1.4, 1.6      |               |               |
| 57296       | Psmd8, proteasome (prosome, macropain) 26S       | 1.5, 1.5      |               |               |
| 11652       | Akt2, thymoma viral proto-oncogene 2             | 1.6           |               |               |
| 21781       | Tfdp1, transcription factor Dp 1                 | 1.5           |               |               |

**Cytoskeleton**

| Gene Symbol | Description                                      | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|-------------|--------------------------------------------------|---------------|---------------|---------------|
| 22151       | Tubb2, tubulin, beta 2                           | 7.9, 6.7      |               |               |
| 22143       | Tuba2, tubulin, alpha 2                          | 2.5, 5.1      |               |               |
| 22146       | Tuba6, tubulin, alpha 6                          | 2.3, 4.4      |               |               |
| 16668       | Krt1-18, keratin complex 1, acidic, gene 18      | 1.6, 6.2      |               |               |
| 22154       | Tubb5, tubulin, beta 5                           | 2.8, 3.9      |               |               |
| 22145       | Tuba4, tubulin, alpha 4                          | 2.6           |               |               |
| 69654       | Dctn2, dynactin 2                                 | 1.5, 2.6      |               |               |
| 11465       | Actg1, actin, gamma, cytoplasmic 1                | 2.6, 2.2, 2.3 |               |               |
| 56191       | Tro, trophinin                                    | 2.2           |               |               |
| 11461       | Actb, actin, beta, cytoplasmic                    | 2.4, 2.0      |               |               |
| 11475       | Acta2, actin, alpha 2, smooth muscle, aorta      | 2.3, 2.0      |               |               |
| 22003       | Tpm1, tropomyosin 1, alpha                        | 2.1, 2.2      |               |               |
| 12317       | Calr, calreticulin                               | 1.9           |               |               |
| 19241       | Tmsb4x, thymosin, beta 4, X chromosome            | 1.8, 2.0      |               |               |
| 12331       | Cap1, CAP, adenylate cyclase-associated protein 1| 2.0           |               |               |
| 94179       | Krt1-23, keratin complex 1, acidic, gene 23      | 1.7, 1.9      |               |               |
| 13589       | Mapre1, microtubule-associated protein, RP/EB    | 1.7           |               |               |
| 13800       | Enah, enabled homolog (Drosophila)               | -1.7, -1.4, -1.8 |         |               |
| 18643       | Pfn1, profilin 1                                  | 1.5, 1.6      |               |               |
| Gene ID  | Gene Symbol | Description | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|---------|-------------|-------------|---------------|---------------|---------------|
| 12631   | Cfl1        | cofilin 1, non-muscle | 1.7           |               |               |
| 17904   | Myl6        | myosin, light polypeptide 6, alkali, smooth muscle and non-muscle | 1.8           |               |               |
| 20742   | Spnb2       | spectrin beta 2 | 1.6           |               |               |
| 22388   | Wdr1        | WD repeat domain 1 | 1.4           | 1.7           |               |
| 67938   | Mylc2b      | myosin light chain, regulatory B | 1.7           |               |               |
| 16905   | Lmna        | lamin A | 1.3           | 1.6           |               |
| 16691   | Krt2-8      | keratin complex 2, basic, gene 8 | 1.6           | 1.7           |               |
| 13007   | Csrp1       | cysteine and glycine-rich protein 1 | 1.4           | 1.6           |               |
| 59069   | Tpm3        | tropomyosin 3, gamma |               |               | 1.5           |
| 17920   | Myo6        | myosin VI | -1.5          | -1.3          | -1.4          |
| 21648   | Tctex1      | t-complex testis expressed 1 | 1.4           | 1.5           |               |

**Fatty acid metabolism**

| Gene ID  | Gene Symbol | Description | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|---------|-------------|-------------|---------------|---------------|---------------|
| 11364   | Acadm       | acetyl-Coenzyme A dehydrogenase, medium chain | 3.7           |               |               |
| 14081   | Acsl1       | acyl-CoA synthetase long-chain family member 1 | -1.7          | -3.6          |               |
| 170439  | Elovl6      | ELOVL family member 6, elongation of long chain fatty acids (yeast) | 2.4           | 2.3           |               |
| 16922   | Phyh        | phytanoyl-CoA hydroxylase | -1.9          | -1.9          | -2.1          |
| 111175  | Pecr        | peroxisomal trans-2-enoyl-CoA reductase | -2.1          | -1.7          |               |
| 20216   | Sah         | SA rat hypertension-associated homolog | -1.4          | -1.6          | -1.7          |
| 93747   | Echs1       | enoyl Coenzyme A hydratase, short chain, 1, mitochondrial | -1.5          |               |               |
| 66885   | Acadsb      | acyl-Coenzyme A dehydrogenase, short/branched chain | -1.4          | -1.6          |               |

**Immune response**

| Gene ID  | Gene Symbol | Description | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|---------|-------------|-------------|---------------|---------------|---------------|
| 20315   | Cxcl12      | chemokine (C-X-C motif) ligand 12 | -2.2          |               |               |
| 12475   | Cd14        | CD14 antigen |               |               | 2.2           |
| 80859   | Nfkbiz      | nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta | 2.0           | 1.3           |               |
| 18489   | Pap         | pancreatitis-associated protein |               |               | 1.9           |
| 12010   | B2m         | beta-2 microglobulin | -1.7          | -1.7          |               |
| 50909   | C1r         | complement component 1, r subcomponent |               |               | -1.5          |

**Lipid metabolism**

| Gene ID  | Gene Symbol | Description | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|---------|-------------|-------------|---------------|---------------|---------------|
| 20209   | Saa2        | serum amyloid A 2 | 3.6           | 67.3          | 83.4          |
| 11808   | Apoa4       | apolipoprotein A-IV |               | 23.6          | 21.3          |
| 69060   | Pnlip       | pancreatic lipase  | 7.1           | 2.6           |               |
| 11520   | Adfp        | adipose differentiation related protein | 4.6           | 1.7           |               |
| 18946   | Pnliprp1    | pancreatic lipase related protein 1 | 2.9           | 3.7           |               |
| 109791  | Clps        | colipase, pancreatic |               |               | 2.1           |
| 14137   | Fdft1       | farnesyl diphosphate farnesyl transferase 1 |               | -2.8          |               |
| 11807   | Apoa2       | apolipoprotein A-II | -1.9          | -2.6          |               |
| 171210  | MGI:2159605 | mitochondrial acyl-CoA thioesterase 1 | 2.4           | 1.8           |               |
| 15450   | Lipc        | lipase, hepatic | -2.2          | -1.5          |               |
| 12613   | Cel         | carboxyl ester lipase |               | 2.4           |               |
| 11813   | Apoc2       | apolipoprotein C-II | 1.6           | 2.3           |               |
| 18534   | Pck1        | phosphoenolpyruvate carboxykinase 1, cytosolic | 1.6           | 2.3           |               |
| Gene ID  | Gene Description                          | log2 Fold Change |
|---------|-------------------------------------------|------------------|
| 56794   | RIKEN cDNA 1600020H07 gene                | 1.7              |
| 13641   | ephrin B1                                 | -1.6             |
| 21991   | triosephosphate isomerase 1              | 1.8              |
| 20280   | sterol carrier protein 2, liver          | -2.0             |
| 11657   | albumin 1                                | 1.9              |
| 14824   | granulin                                 | 1.5, 1.9         |
| 14080   | fatty acid binding protein 1, liver      | -1.5, -1.7       |
| 66113   | apolipoprotein A-V                       | 1.5, 1.5         |
| 68465   | adiponectin receptor 2                   | -1.5             |
| 228033  | ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (subunit 9), isoform 3 | 1.5 |

**Metabolism - other**

| Gene ID  | Gene Description                          | log2 Fold Change |
|---------|-------------------------------------------|------------------|
| 68449   | RIKEN cDNA 1110003P22 gene                | 1.5              |
| 12350   | carbonic anhydrase 3                      | -21.0, -15.5     |
| 11723   | amylase 2, pancreatic                     | 7.1, 6.2         |
| 11522   | alcohol dehydrogenase 1 (class I)        | -4.5             |
| 231691  | serine dehydratase                        | -2.5, -3.6       |
| 18979   | paraoxonase 1                             | -2.5, -2.2       |
| 14871   | glutathione S-transferase, theta 1        | 1.5, -2.0, -1.5  |
| 22262   | urate oxidase                             | -2.9, -2.3       |
| 14635   | galactokinase 1                           | 2.8, 1.8         |
| 109801  | glyoxalase 1                              | -2.1, -2.6, -2.0 |
| 14857   | glutathione S-transferase, alpha 1 (Ya)   | -2.5             |
| 68021   | biphenyl hydrolase-like (serine hydrolase, breast epithelial mucin-associated antigen) | -1.9, -1.8 |
| 19193   | pipelolic acid oxidase                    | -2.3, -1.7       |
| 14863   | glutathione S-transferase, mu 2           | -1.8, -2.0       |
| 14862   | glutathione S-transferase, mu 1           | -1.8, -1.9       |
| 14068   | coagulation factor VII                    | -2.1             |
| 11720   | methionine adenosyltransferase I, alpha   | 2.1, 1.4         |
| 12349   | carbonic anhydrase 2                      | -2.0             |
| 11668   | aldehyde dehydrogenase family 1, subfamily A1 | -1.6, -2.0, -1.5 |
| 94284   | UDP glycosyltransferase 1 family, polypeptide A6 | -1.8, -1.8 |
| 20148   | dehydrogenase/reductase (SDR family) member 3 | -2.0, -1.6 |
| 100727  | expressed sequence AI788959              | -1.9             |
| 104444  | small fragment nuclease                   | 1.7              |
| 58875   | 3-hydroxyisobutyrate dehydrogenase       | -1.8, -1.6       |
| 22187   | ubiquitin B                              | 1.8              |
| 20775   | squalene epoxidase                       | -1.6, -1.8       |
| 232223  | thioredoxin reductase 3                   | -1.8, -1.7       |
| 15199   | heme binding protein 1                   | -1.6             |
| 216558  | UDP-glucose pyrophosphorylase 2           | -1.5             |
| 12346   | carbonic anhydrase 1                      | -1.7, -1.7       |
| 16333   | insulin I                                | 1.5              |
| 11867   | actin related protein 2/3 complex, subunit 1B | 1.7, 1.5 |

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| Accession | Gene Symbol | Description                                                                                             | Fold Change |
|-----------|-------------|---------------------------------------------------------------------------------------------------------|--------------|
| 67895     | Pyp         | pyrophosphatase stress 70 protein chaperone, microsome-associated, human homolog                        | 1.5          |
| 110920    | Stch        | stress 70 protein chaperone, microsome-associated, human homolog                                        | 1.7          |
| 209558    | Enpp3       | ectonucleotide pyrophosphatase/phosphodiesterase 3                                                      | -1.6         |
| 110695    | Aldh7a1     | aldehyde dehydrogenase family 7, member A1                                                              | -1.6         |
| 12468     | Cct7        | chaperonin subunit 7 (eta)                                                                              | 1.6          |
| 15446     | Hpgd        | hydroxyprostaglandin dehydrogenase 15 (NAD)                                                              | 1.6          |
| 319625    | Galm        | galactose mutarotase                                                                                    | -1.5         |
| 110821    | Pcca        | propionyl-Coenzyme A carboxylase, alpha polypeptide                                                      | -1.5         |
| 55990     | Fmo2        | flavin containing monooxygenase 2                                                                        | 1.5          |

### Miscellaneous binding

| Accession | Gene Symbol | Description                                                                                             | Fold Change |
|-----------|-------------|---------------------------------------------------------------------------------------------------------|--------------|
| 19692     | Reg1        | regenerating islet-derived 1                                                                            | 7.3          |
| 19693     | Reg2        | regenerating islet-derived 2                                                                            | 5.4          |
| 20341     | Selenbp1    | selenium binding protein 1                                                                              | -3.1         |
| 57436     | Gabarapl1   | gamma-aminobutyric acid (GABA(A)) receptor-associated protein-like 1                                      | -3.1         |
| 20219     | Apcs        | serum amyloid P-component                                                                               | 1.9          |
| 73710     | 2410129E14Rik | RIKEN cDNA 2410129E14 gene                                                                               | 3.4          |
| 72999     | Insig2      | insulin induced gene 2                                                                                  | 2.2          |
| 54208     | Arl6ip1     | ADP-ribosylation factor-like 6 interacting protein 1                                                      | -1.9         |
| 23950     | Dnajb6      | DnaJ (Hsp40) homolog, subfamily B, member 6                                                               | 2.1          |
| 22329     | Vcam1       | vascular cell adhesion molecule 1                                                                        | 1.6          |
| 83997     | Slmap       | sarcolemma associated protein                                                                            | -1.7         |
| 93684     | MGI:1927947 | selenoprotein                                                                                            | 1.7          |
| 17524     | Mpp1        | membrane protein, palmitoylated                                                                          | 1.4          |

### Protein biosynthesis

| Accession | Gene Symbol | Description | Fold Change |
|-----------|-------------|-------------|-------------|
| 110954    | Rpl10       | ribosomal protein 10                                   | 1.3          |
| 67945     | Rpl41       | ribosomal protein 14                                   | 1.3          |
| 269261    | Rpl12       | ribosomal protein 12                                   | 1.9          |
| 27050     | Rps3        | ribosomal protein 3                                    | 1.3          |
| 26961     | Rpl8        | ribosomal protein 8                                    | 2.1          |
| 20116     | Rps8        | ribosomal protein 8                                    | 1.3          |
| 20005     | Rpl9        | ribosomal protein 9                                    | 1.7          |
| 22121     | Rpl13a      | ribosomal protein 13a                                  | 1.6          |
| 27367     | Rpl3        | ribosomal protein 3                                    | 1.8          |
| 20055     | Rps16       | ribosomal protein 16                                   | 1.5          |
| 20042     | Rps12       | ribosomal protein 12                                   | 1.9          |
| 54127     | Rps28       | ribosomal protein 28                                   | 1.9          |
| 319195    | Rpl17       | ribosomal protein 17                                   | 1.4          |
| 27207     | Rps11       | ribosomal protein 11                                   | 1.3          |
| 27176     | Rpl7a       | ribosomal protein 7a                                   | 1.8          |
| 56040     | Rplp1       | ribosomal protein, large, P1                           | 1.8          |
| 20088     | Rps24       | ribosomal protein 24                                   | 1.7          |
| 67097     | Rps10       | ribosomal protein 10                                   | 1.7          |
| Gene Name | Description | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|-----------|-------------|---------------|---------------|---------------|
| Rpl39     | ribosomal protein L39 | 1.7 | | |
| Rpl18     | ribosomal protein L18 | 1.7 | | |
| Rps19     | ribosomal protein S19 | 1.7 | | |
| Rpl11     | ribosomal protein L11 | 1.7 | 1.4 | |
| Rps4x     | ribosomal protein S4, X-linked | 1.7 | | |
| Rpl27a    | ribosomal protein L27a | 1.6 | | |
| Rps5      | ribosomal protein S5 | 1.3 | 1.6 | |
| Rpl7      | ribosomal protein L7 | 1.6 | | |
| Rps20     | ribosomal protein S20 | 1.4 | | |
| Rpl29     | ribosomal protein L29 | 1.4 | 1.5 | |
| Rps7      | ribosomal protein S7 | 1.3 | 1.6 | |
| Rps15a    | ribosomal protein S15a | 1.4 | 1.5 | |
| Rpl19     | ribosomal protein L19 | 1.5 | | |
| Rps27a    | ribosomal protein S27a | 1.5 | | |
| Lamr1     | laminin receptor 1 (ribosomal protein SA) | 1.5 | 2.6 | |
| Eif3s9    | eukaryotic translation initiation factor 3, subunit 9 (eta) | 2.1 | 1.7 | |
| Arbp      | acidic ribosomal phosphoprotein P0 | 1.5 | 2.2 | |
| Eif4a1    | eukaryotic translation initiation factor 4A1 | 1.7 | 1.6 | |
| Eef1b2    | eukaryotic translation elongation factor 1 beta 2 | 1.3 | 1.7 | |
| Eif2ak1   | eukaryotic translation initiation factor 2 alpha kinase 1 | 1.4 | 1.7 | |
| Eif4a2    | eukaryotic translation initiation factor 4A2 | -1.6 | | |
| Rps9      | ribosomal protein S9 | 1.6 | | |
| Eif2s3x   | eukaryotic translation initiation factor 2, subunit 3, structural gene X-linked | 1.3 | 1.5 | |
| Rpl18a    | Ribosomal protein L18A | 1.4 | 1.5 | |
| Eef1d     | eukaryotic translation elongation factor 1 delta (guanine nucleotide exchange protein) | 1.3 | 1.5 | |
| Ywhaz     | tyrosine 3-monooxygenase/trypotphan 5-monooxygenase activation protein, zeta polypeptide | 1.3 | 1.7 | |

**Signal transduction**

| Gene Name | Description | Fold Change 1 | Fold Change 2 | Fold Change 3 |
|-----------|-------------|---------------|---------------|---------------|
| Mt2       | metallothionein 2 | 9.2 | 2.6 | 4.3 |
| Mt1       | metallothionein 1 | 6.5 | 2.7 | 4.2 |
| Rab34     | RAB34, member of RAS oncogene family | | | 5.4 |
| Rab1      | RAB1, member RAS oncogene family | | | 2.9 |
| Sort1     | sortilin 1 | | | 3.0 |
| Pigr      | polymeric immunoglobulin receptor | -2.3 | -3.3 | |
| Gnbp2     | guanine nucleotide binding protein, beta 2 | | | 3.1 |
| Dusp22    | dual specificity phosphatase 22 | | | 1.7 |
| Grb2      | growth factor receptor bound protein 2 | -2.0 | -2.5 | |
| Dmbt1     | deleted in malignant brain tumors 1 | | | 2.1 |
| 5730406l15Rik | RIKEN cDNA 5730406l15 gene | 2.2 | | 2.4 |
| Igf1      | insulin-like growth factor 1 | | | -2.4 |
| Spp1      | secreted phosphoprotein 1 | | | 2.1 |
| Ptk2      | PTK2 protein tyrosine kinase 2 | | | 2.2 |
| Ctgf      | connective tissue growth factor | 1.3 | 1.9 | 2.1 |
| Srpr      | signal recognition particle receptor (‘docking protein’) | -1.6 | -2.0 | |
| Gene Symbol | Gene Name | Expression Level 1 | Expression Level 2 | Expression Level 3 |
|------------|-----------|--------------------|--------------------|--------------------|
| AW742319   | expressed sequence AW742319 | 1.8 | 1.5 | |
| Gnb2-rs1   | guanine nucleotide binding protein, beta 2, related sequence 1 | 1.6 | 1.9 | |
| Pgrmc1     | progesterone receptor membrane component 1 | 1.9 | |
| Ywhaq      | tyrosine 3-monoxygenase/tryptophan 5-monoxygenase activation protein, theta polypeptide | 1.8 | 1.4 | 1.8 |
| Ptprz1     | protein tyrosine phosphatase, receptor type Z, polypeptide 1 | 1.5 | |
| Dek        | DEK oncogene (DNA binding) | 1.6 | |
| Bzrp       | benzodiazepine receptor, peripheral | 1.7 | |
| Dtx3       | deltex 3 homolog (Drosophila) | 1.7 | |
| Ssr2       | signal sequence receptor, beta | 1.3 | 1.6 | |
| Gab1       | growth factor receptor bound protein 2-associated protein 1 | 1.7 | |
| Stat5a     | signal transducer and activator of transcription 5A | 1.7 | 1.5 | |
| Bcap37     | B-cell receptor-associated protein 37 | 1.5 | 1.8 | |
| Pvr2       | poliovirus receptor-related 2 | 1.6 | 1.5 | |
| Wnt3a      | wingless-related MMTV integration site 3A | 1.5 | |
| Prkcb1     | protein kinase C, beta 1 | 1.5 | |
| Arf4       | ADP-ribosylation factor 4 | 1.6 | |
| Dscrl      | Down syndrome critical region homolog 1 (human) | 1.5 | |
| A1cam      | activated leukocyte cell adhesion molecule | 1.5 | 1.5 | |
| Tceal8     | transcription elongation factor A (SII)-like 8 | 1.4 | 1.6 | 1.4 |
| Fzd4       | frizzled homolog 4 (Drosophila) | -1.6 | |
| Rassf3     | Ras association (RalGDS/AF-6) domain family 3 | 1.6 | |
| Tomm20     | translocase of outer mitochondrial membrane 20 homolog (yeast) | 1.5 | |
| Racgap1    | Rac GTPase-activating protein 1 | 1.5 | |
| Hcph       | hemopoietic cell phosphatase | 1.5 | |

**Steroid metabolism**

| Gene Symbol | Gene Name | Expression Level 1 | Expression Level 2 | Expression Level 3 |
|------------|-----------|--------------------|--------------------|--------------------|
| Hsd3b4     | hydroxysteroid dehydrogenase-4, delta<5>-3-beta | -4.3 | -9.0 | -4.5 |
| Sc4mol     | sterol-C4-methyl oxidase-like | -5.0 | -3.3 | |
| Hsd3b1     | hydroxysteroid dehydrogenase-1, delta<5>-3-beta | -2.4 | -3.6 | -3.0 |
| Idi1       | isopentenyl-diphosphate delta isomerase | -3.6 | -1.8 | |
| Akr1c20    | aldo-keto reductase family 1, member C20 | -2.8 | |
| Hmgcs1     | 3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1 | -2.1 | -1.7 | |
| Ttr        | transthyretin | -2.0 | |

**Stress response**

| Gene Symbol | Gene Name | Expression Level 1 | Expression Level 2 | Expression Level 3 |
|------------|-----------|--------------------|--------------------|--------------------|
| Cat        | catalase | -1.8 | -2.4 | -3.0 |
| Fn1        | fibronectin 1 | 2.6 | |
| Prkra      | protein kinase, interferon inducible double stranded RNA dependent activator | 2.4 | |
| Hspca      | heat shock protein 1, alpha | 2.1 | 1.6 | |
| Idh1       | isocitrate dehydrogenase 1 (NADP+), soluble | -2.0 | |
| Serpina1a  | serine (or cysteine) proteinase inhibitor, clade A, member 1a | -1.9 | -1.4 | |
| Anxa2      | annexin A2 | 1.8 | 2.2 | |
| Gene ID | Description | Log2 Fold Change | Log10 Fold Change |
|--------|-------------|----------------|-----------------|
| 20701  | Serpina1b   | -1.6           | -1.3            |
| 15505  | Hsp105      |                | 1.5             |

**Transcription**

| Gene ID | Description                                                                 | Log2 Fold Change | Log10 Fold Change |
|--------|----------------------------------------------------------------------------|----------------|-----------------|
| 19014  | Pparbp peroxisome proliferator activated receptor binding protein           | 18.1            | 9.2             |
| 22642  | Zbtb17 zinc finger and BTB domain containing 17                              | 6.0             |                 |
| 15184  | Hdac5 histone deacetylase 5                                                | 4.8             |                 |
| 232807 | Ppp1r12c protein phosphatase 1, regulatory (inhibitor) subunit 12C          | 5.7             | 4.0             |
| 13653  | Egr1 early growth response 1                                               | 4.8             | 2.0             |
| 15081  | H3f3b H3 histone, family 3B                                                | 4.6             | 2.3             |
| 51788  | H2afz H2A histone family, member Z                                         | 3.0             |                 |
| 12608  | Cebpb CCAAT/enhancer binding protein (C/EBP), beta splicing factor proline/glutamine rich (polypyrimidine tract binding protein associated) | 3.6             | 2.2             |
| 71514  | Sfpq                                                                       | 3.3             |                 |
| 19205  | Ptbp1 polypyrimidine tract binding protein 1                               | 3.0             |                 |
| 17692  | Msli1 male-specific lethal-3 homolog 1 (Drosophila)                        | 2.9             |                 |
| 21815  | Tgif TG interacting factor                                                 | 3.4             |                 |
| 20018  | Rpo1-3 RNA polymerase 1-3                                                 | 2.8             |                 |
| 59687  | Hmg20a high mobility group 20A                                             | 2.6             |                 |
| 229584 | Pogz pogo transposable element with ZNF domain                             | 2.2             |                 |
| 19652  | Rbm3 RNA binding motif protein 3                                           | 2.7             | 1.9             |
| 20595  | Smn1 survival motor neuron 1                                               | 2.6             |                 |
| 97165  | Hmgb2 high mobility group box 2                                            | 2.4             |                 |
| 58809  | Rnase4 ribonuclease, RNase A family 4                                      | 2.1             |                 |
| 64050  | Yeats4 YEATS domain containing 4                                           | 1.9             |                 |
| 21807  | Tgb1i4 transforming growth factor beta 1 induced transcript 4              | -2.2            | -1.8            |
| 193116 | D11Ertd730e DNA segment, Chr 11, ERATO Doi 730, expressed                 | 2.1             |                 |
| 15331  | Hmgn2 high mobility group nucleosomal binding domain 2                     | 2.1             |                 |
| 19752  | Rnase1 ribonuclease, RNase A family 1 (pancreatic)                         | 2.1             |                 |
| 52705  | Hrb2 HIV-1 Rev binding protein 2                                           | 1.7             |                 |
| 213742 | Xist inactive X specific transcripts                                       | 1.8             | 2.0             |
| 64384  | Sirt3 sirtuin 3 (silent mating type information regulation 2, homolog) 3 (S. cerevisiae) | 2.0             |                 |
| 20220  | Sap18 Sin3-associated polypeptide 18                                        | 2.0             |                 |
| 20384  | Sf5s5 splicing factor, arginine/serine-rich 5 (SRp40, HRS)                | 1.6             |                 |
| 192657 | EII2 elongation factor RNA polymerase II 2                                 | 1.9             | 1.2             |
| 67996  | Sf56 splicing factor, arginine/serine-rich 6                                | 1.9             |                 |
| 18813  | Pa2g4 proliferation-associated 2G4                                          | 1.7             |                 |
| 26356  | Ing1 inhibitor of growth family, member 1                                  | 1.8             |                 |
| 20383  | Sf53 splicing factor, arginine/serine-rich 3 (SRp20)                       | 1.8             |                 |
| 105559 | Mbnl2 muscleblind-like 2                                                   | 1.7             | 1.8             |
| 229279 | Hnrpa3 heterogeneous nuclear ribonucleoprotein A3                          | 1.8             |                 |
| 15377  | Foxa3 forkhead box A3                                                     | 1.8             |                 |
| 15078  | H3f3a H3 histone, family 3A                                                | 1.6             |                 |
| 80898  | MGI:1933403 type 1 tumor necrosis factor receptor shedding aminopeptidase regulator | -1.7            | -1.5            |
| Gene ID | Description | Log2 Fold Change 1 | Log2 Fold Change 2 | Log2 Fold Change 3 |
|---------|-------------|--------------------|--------------------|--------------------|
| 272359  | Irf2bp1 interferon regulatory factor 2 binding protein 1 | -1.7 | -1.5 | |
| 192231  | MGI:2385923 cardiac lineage protein 1 | | | |
| 53605   | Nap11 nucleosome assembly protein 1-like 1 | 1.5 | 1.6 | |
| 15384   | Hnrpab heterogeneous nuclear ribonucleoprotein A/B | | | |
| 16599   | Klf3 Kruppel-like factor 3 (basic) | 1.6 | | |
| 11804   | Aplp2 amyloid beta (A4) precursor-like protein 2 | | -1.6 | |
| 68278   | Ddx39 DEAD (Asp-Glu-Ala-Asp) box polypeptide 39 | | 1.6 | |
| 18148   | Npm1 nucleophosmin 1 | 1.2 | 1.4 | 1.6 |
| 13207   | Ddx5 DEAD (Asp-Glu-Ala-Asp) box polypeptide 5 | | 1.6 | |
| 51886   | Fubp1 far upstream element (FUSE) binding protein 1 | | | |
| 15901   | Idb1 inhibitor of DNA binding 1 | | | |
| 59028   | Rcl1 RNA terminal phosphate cyclase-like 1 | -1.5 | -1.4 | |
| 13496   | Arid3a AT rich interactive domain 3A (Bright like) | 1.3 | | 1.5 |

**Transport and storage**

| Gene ID | Description | Log2 Fold Change 1 | Log2 Fold Change 2 | Log2 Fold Change 3 |
|---------|-------------|--------------------|--------------------|--------------------|
| 16819   | Lcn2 lipocalin 2 | 3.3 | 120.7 | 49.6 |
| 22072   | Prss2 protease, serine, 2 | | 7.3 | 14.0 |
| 12401   | Serpina6 serine (or cysteine) proteinase inhibitor, clade A, member 6 | | -8.1 | -2.3 |
| 14262   | Fmo3 flavin containing monooxygenase 3 | 8.8 | | 1.2 |
| 13107   | Cyp2f2 cytochrome P450, family 2, subfamily f, polypeptide 2 | -2.8 | -4.2 | -6.9 |
| 22327   | Vbp1 von Hippel-Lindau binding protein 1 | | | 3.9 |
| 13099   | Cyp2c40 cytochrome P450, family 2, subfamily c, polypeptide 40 | 1.5 | -3.2 | -2.6 |
| 104158  | Ces3 carboxylesterase 3 | | -3.2 | -2.1 |
| 17836   | Mug1 murinoglobulin 1 | -2.7 | -1.9 | -4.0 |
| 100561  | Slc15a4 solute carrier family 15, member 4 | | | 3.8 |
| 13117   | Cyp4a10 cytochrome P450, family 4, subfamily a, polypeptide 10 | 2.0 | | |
| 78388   | Mvp major vault protein | | | |
| 16647   | Kpnal karyopherin (importin) alpha 2 | | | |
| 13884   | Es1 esterase 1 | 1.7 | 3.1 | 1.9 |
| 67760   | Slc38a2 solute carrier family 38, member 2 | 2.8 | | |
| 71519   | Cyp2u1 cytochrome P450, family 2, subfamily u, polypeptide 1 | 2.5 | | |
| 70231   | Gorasp2 golgi reassembly stacking protein 2 | 2.3 | | 2.6 |
| 71393   | Kctd6 potassium channel tetramerisation domain containing 6 | | 1.6 | |
| 69354   | Slc38a4 solute carrier family 38, member 4 | | -2.1 | -2.7 |
| 21817   | Tgm2 transglutaminase 2, C polypeptide | | 2.7 | 2.6 |
| 11747   | Anxa5 annexin A5 | 1.6 | 2.0 | 2.5 |
| 20194   | S100a10 S100 calcium binding protein A10 (calpactin) | 1.6 | 2.4 | 1.8 |
| 50527   | Ero1l ERO1-like (S. cerevisiae) | | | 1.6 |
| 66427   | 1810044O22Rik RIKEN cDNA 1810044O22 gene | -1.6 | | -2.1 |
| 18453   | P4hb prolyl 4-hydroxylase, beta polypeptide | 2.1 | | 1.9 |
| 22228   | Ucp2 uncoupling protein 2, mitochondrial | 2.3 | 2.3 | 1.9 |
| 19128   | Pros1 protein S (alpha) | 2.2 | | 1.4 |
| 20501   | Scl16a1 solute carrier family 16 (monocarboxylic acid transporters), member 1 | 2.2 | 2.2 | 2.1 |
| 11931   | Atp1b1 ATPase, Na+/K+ transporting, beta 1 polypeptide | 2.2 | | |
| 56185   | Hao3 hydroxyacid oxidase (glycolate oxidase) 3 | 2.0 | | |
| Gene ID | Gene Name                  | Description                                                                 | Fold Change |
|--------|----------------------------|-----------------------------------------------------------------------------|-------------|
| 12560  | Cdh3                       | cadherin 3                                                                  | 2.1         |
| 13101  | Cyp2d10                    | cytochrome P450, family 2, subfamily d, polypeptide 10                       | -1.7        |
| 12555  | Cdh15                      | cadherin 15                                                                 | 2.0         |
| 59010  | Sqrdl                      | sulfide quinone reductase-like (yeast)                                       | -1.6        |
| 22027  | Tra1                       | tumor rejection antigen gp96                                                | 1.9         |
| 22334  | Vdac2                      | voltage-dependent anion channel 2                                           | 1.6         |
| 11981  | Atp9a                      | ATPase, class II, type 9A amyloid beta (A4) precursor protein-binding, family A, member 3 | 1.9 |
| 57267  | Apba3                      | TBD                                                                           | 1.8         |
| 74277  | Chic2                      | TBD                                                                            | 1.4         |
| 66576  | Uqcrh                      | TBD                                                                            | 1.8         |
| 12499  | Entpd5                     | TBD                                                                            | -1.7        |
| 56448  | Cyp2d22                    | cytochrome P450, family 2, subfamily d, polypeptide 22                       | -1.7        |
| 11778  | Ap3s2                      | TBD                                                                            | 1.6         |
| 29876  | Clic4                      | chloride intracellular channel 4 (mitochondrial)                            | 1.6         |
| 18984  | Por                        | TBD                                                                            | 1.6         |
| 229782 | Slc35a3                    | solute carrier family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) transporter), member 3 | -1.7 |
| 20692  | Sparc                      | secreted acidic cysteine rich glycoprotein                                  | 1.7         |
| 21366  | Slc6a6                     | TBD                                                                            | 1.6         |
| 68267  | Slc25a22                   | TBD                                                                            | 1.5         |
| 54403  | Slc4a4                     | solute carrier family 4 (anion exchanger), member 4                         | 1.6         |
| 11699  | Ambp                       | TBD                                                                            | 1.6         |
| 74129  | Dmgdh                      | dimethylglycine dehydrogenase precursor                                      | -1.6        |
| 11833  | Aqp8                       | TBD                                                                            | -1.6        |
| 26458  | Slc27a2                    | solute carrier family 27 (fatty acid transporter), member 2                 | -1.6        |
| 56188  | Fxyd1                      | FXYD domain-containing ion transport regulator 1                             | -1.5        |
| 110826 | Ettb                       | TBD                                                                            | 1.5         |
| 15382  | Hnrpa1                     | heterogeneous nuclear ribonucleoprotein A1                                   | 1.5         |
| 11927  | Atox1                      | TBD                                                                            | 1.5         |
| 12330  | Canx                       | TBD                                                                            | -1.5        |
| 102866 | PIs3                       | TBD                                                                            | -1.4        |
| 68421  | RIKEN cDNA 0910001K20      | RIKEN cDNA 0910001K20 gene                                                   | 6.6         |
| 15982  | Ifrd1                      | interferon-related developmental regulator 1                                | 1.6         |
| 83797  | Smarcd1                    | TBD                                                                            | 3.2         |
| 19231  | Ptma                       | TBD                                                                            | 2.2         |
| 30924  | Angptl3                    | angiopoietin-like 3                                                          | -2.5        |
| 15902  | Igb2                       | TBD                                                                            | -2.2        |
| 69071  | RIKEN cDNA 1810014L12      | RIKEN cDNA 1810014L12 gene                                                   | -2.1        |
| 68801  | ElovL5                     | TBD                                                                            | 2.3         |
| 74840  | Armet                      | TBD                                                                            | 1.6         |
| 73046  | RIKEN cDNA 2900070E19      | TBD                                                                            | 2.0         |

**Other**

| Gene ID | Gene Name                  | Description                                                                 | Fold Change |
|--------|----------------------------|-----------------------------------------------------------------------------|-------------|
| 68421  | RIKEN cDNA 1810014L12      | TBD                                                                            | -2.1        |
| 68801  | ElovL5                     | TBD                                                                            | 2.3         |
| 74840  | Armet                      | arginine-rich, mutated in early stage tumors                                | 1.6         |
| 73046  | RIKEN cDNA 2900070E19      | TBD                                                                            | 2.0         |
| Gene ID | Gene Name | Description                                                                 | Value  |
|---------|-----------|------------------------------------------------------------------------------|--------|
| 71733   | Susd2     | sushi domain containing 2                                                    | 1.6    |
| 218335  | C130052I12Rik | RIKEN cDNA C130052I12 gene                                                   | 2.0    |
| 66087   | 0610039A15Rik | RIKEN cDNA 0610039A15 gene                                                  | 1.9    |
| 22242   | Umod      | uromodulin                                                                  | 1.9    |
| 56424   | Stub1     | STIP1 homology and U-Box containing protein 1                               | 1.5    |
| 98238   | AA959742  | expressed sequence AA959742                                                 | 1.8    |
| 192662  | Arhgd1a   | Rho GDP dissociation inhibitor (GDI) alpha                                   | 1.8    |
| 67125   | Sas       | sarcoma amplified sequence                                                  | 1.6    |
| 67226   | Tmem19    | transmembrane protein 1                                                     | 1.7    |
| 80876   | Ifitm2    | interferon induced transmembrane protein 2                                  | 1.4    |
| 67154   | Mtsh      | Metadherin                                                                  | 1.7    |
| 12512   | Cd63      | Cd63 antigen                                                                | 1.7    |
| 217864  | D12Wsu95e | DNA segment, Chr 12, Wayne State University 95, expressed                    | 1.7    |
| 58520   | 0610007P14Rik | RIKEN cDNA 0610007P14 gene                                                  | -1.6   |
| 380712  | 2010305C02Rik | RIKEN cDNA 2010305C02 gene                                                 | -1.6   |
| 50884   | Nckap1    | NCK-associated protein 1                                                    | -1.6   |
| 68581   | 1110014C03Rik | RIKEN cDNA 1110014C03 gene                                                 | 1.5    |
| 67067   | 2010100O12Rik | RIKEN cDNA 2010100O12 gene                                                 | -1.6   |
| 269831  | Tm4sf12   | transmembrane 4 superfamily member 12                                       | -1.6   |
| 68539   | 1110006I15Rik | RIKEN cDNA 1110006I15 gene                                                 | 1.5    |
| 52469   | D11Erd99e | DNA segment, Chr 11, ERATO Doi 99, expressed                               | 1.5    |
| 78330   | 1500032D16Rik | RIKEN cDNA 1500032D16 gene                                                 | -1.5   |
|         | Unknown   |                                                                              |        |
| 100620  | AI413194  | expressed sequence AI413194                                                 | 14.2   |
| 234199  | Fgl1      | fibrinogen-like protein 1                                                    | 3.5    |
|         |          |                                                                               | 12.5   |
|         |          |                                                                               | 8.8    |
| -       |          |                                                                               | 11.9   |
|         |          |                                                                               | 1.9    |
|         |          |                                                                               | 6.2    |
| -       |          |                                                                               | 0      |
| -       |          |                                                                               | 8.4    |
| -       |          |                                                                               | 5.3    |
|         |          |                                                                               | 9.9    |
| 76799   | 2510006D16Rik | RIKEN cDNA 2510006D16 gene                                                | 7.6    |
| 22073   | Prss3     | protease, serine, 3                                                         | 6.0    |
| 76884   | Cyfip2    | cytoplasmic FMR1 interacting protein 2                                       | 7.1    |
| 269023  | Zfp608    | zinc finger protein 608                                                      | 4.8    |
| -       |          |                                                                               | 6.4    |
| -       |          |                                                                               | 3.4    |
| 108958  | 5730472N09Rik | RIKEN cDNA 5730472N09 gene                                                | 4.8    |
| 14869   | Gstp2     | glutathione S-transferase, pi 2                                             | 4.8    |
| 69116   | 1810009A16Rik | RIKEN cDNA 1810009A16 gene                                                | 3.9    |
| -       |          |                                                                               | 5.1    |
| -       |          |                                                                               | 3.9    |
| -       |          |                                                                               | 5.4    |
| 233895  | BC006909  | cDNA sequence BC006909                                                      | 5.3    |
| 7039    | TGFA      |                                                                               | 5.2    |
|         |          |                                                                               | 1.4    |
| -       |          |                                                                               | 4.9    |
| 66999   | 1500003D12Rik | RIKEN cDNA 1500003D12 gene                                                | 3.2    |
| 234695  | D130029J02Rik | RIKEN cDNA D130029J02 gene                                                 | 3.4    |
| Number | Description | Gene Name | Expression 1 | Expression 2 | Expression 3 |
|--------|-------------|-----------|--------------|--------------|--------------|
| 66523  | RIKEN cDNA 0610039J04 gene | BI439298  | 4.3          | 2.7          |              |
| 382406 | RIKEN cDNA 4933430F16 gene | BM565240;BM565431 |              |              | 2.5          |
|        | BE303336    | CF583483;CF583482 |              | 3.8          | 4.0          |
|        | BE303336    | CF584313;CF584312 |              |              | 3.7          |
|        | BG142276    |            |              |              | 2.4          |
| 27784  | COMM domain containing 8 | CF584643;CF584642 |              | 3.6          | 2.4          |
| 99929  | TCDD-inducible poly(ADP-ribose) polymerase | 4933430F16 | 3.1          |              | 1.4          |
| 233552 | cDNA sequence BC024955 | CF580643  |              |              |              |
| 66185  | RIKEN cDNA 1110037F02 gene | CF584373;CF584374 | 2.9          |              |              |
| 245828 | trafficking protein particle complex 1 | CF622806;BM730909 |              | 2.3          |              |
| 211660 | cDNA sequence BC055915 | CF580075;BI499921 |              | 2.4          | 1.7          |
| 18938  | protein phosphatase 1, regulatory (inhibitor) subunit 14B | CF580075;BI499921 |              | 2.4          | 1.7          |
| 263406 | cDNA sequence BC030417 | CF580643  |              |              |              |
| 21763  | testis expressed gene 2 | CF622806;BM730909 |              | 2.3          | 2.1          |
| 80884  | melanoma antigen, family D, 2 | BQ085135;BQ084821 |              | 2.8          |              |
| 105171 | arrestin domain containing 3 | - | -2.7         | -2.7         |              |
| 445265 | RIKEN cDNA 1810049H19 gene | BI791706;BI711906 |              | 2.6          |              |
| 66975  | RIKEN cDNA 2410002O22 gene | CF577927;CF577926 |              | 2.6          |              |
| 67091  | RIKEN cDNA 1810073E21 gene | CF580075;BI499921 |              | 2.4          |              |
| 69675  | RIKEN cDNA 2310075M15 gene | CF580075;BI499921 |              | 2.4          |              |
| 103781 | RIKEN cDNA 9030024J15 gene | CF580075;BI499921 |              | 2.4          |              |
| 99650  | RIKEN cDNA 4933434E20 gene | CF580075;BI499921 |              | 2.4          |              |
| 26920  | centrosomal protein 1 | - |              | 2.2          |              |
| 66540  | RIKEN cDNA 3110001A13 gene | BG964835  |              | 2.3          | 2.1          |
| 320262 | RIKEN cDNA A830073O21 gene | CF580075;BI499921 |              | 2.3          |              |
| 66659  | acid phosphatase 6, lysophosphatidic | - | 1.3          | 2.5          |              |
| 230866 | RIKEN cDNA C230096C10 gene | AA030342;AI324228 |              | 2.3          |              |
| 231670 | F-box only protein 21 | - | -1.9         | -2.3         |              |
|        |              | AA030342;AI324228 |              | 2.3          | 1.4          | 1.8          |
| Accession | Description | Expression 1 | Expression 2 | Expression 3 |
|-----------|-------------|-------------|-------------|-------------|
| 330474    | BC057627 cDNA sequence BC057627 | 2.1          |             |             |
|           | -           | 2.1          |             |             |
| 407831    | BC054438 cDNA sequence BC054438 | 2.2          |             |             |
| 69036     | 1810010M01Rik RIKEN cDNA 1810010M01 gene | 1.9          |             |             |
| 216454    | CRAD-L cis-retinol/3alpha hydroxysterol short-chain dehydrogenase-like | -1.9         |             |             |
| 76437     | D11Bwg0414e DNA segment, Chr 11, Brigham & Women's Genetics 0414 expressed | 2.1          | 1.8         |             |
| 22381     | Wbp5 WW domain binding protein 5 | 1.3          | 1.5         | 2.1         |
|           | -           |             |             |             |
| 99692     | Al649393 expressed sequence Al649393 | -1.4         | -1.6        | -2.1        |
| 76719     | 1700081L11Rik RIKEN cDNA 1700081L11 gene | 2.1          |             |             |
| 106585    | Ai447928 expressed sequence Ai447928 | -1.7         | -1.7        |             |
|           | -           | 2.1          |             |             |
| 72007     | 1600019O04Rik RIKEN cDNA 1600019O04 gene | 2.0          | 1.6         |             |
| 76464     | 2310043D08Rik RIKEN cDNA 2310043D08 gene | 1.7          | -1.5        | -1.6        |
| 72289     | 2210401K01Rik RIKEN cDNA 2210401K01 gene | 2.0          |             |             |
| 15936     | Ier2 immediate early response 2 | 1.7          |             |             |
| 216440    | 4632413K17Rik RIKEN cDNA 4632413K17 gene | 1.9          |             |             |
|           | -           |             |             | -1.7        |
| 170773    | AB023957 cDNA sequence AB023957 | 1.5          |             |             |
|           | -           |             |             |             |
| 102747    | D430025H09Rik RIKEN cDNA D430025H09 gene | 1.6          |             |             |
| 16432     | Itm2b integral membrane protein 2B | -1.9         |             |             |
|           | -           |             |             |             |
| 65113     | Ndfip1 Nedd4 family interacting protein 1 | -1.7         | -1.5        |             |
| 66390     | 2310042G06Rik RIKEN cDNA 2310042G06 gene | 1.7          | 1.9         |             |
| 66357     | 2310008M10Rik RIKEN cDNA 2310008M10 gene | 1.5          | 1.9         |             |
|           | -           |             |             | -1.7        |
| 105853    | Mal2 mal, T-cell differentiation protein 2 | 1.6          |             |             |
| 74549     | 9130404D08Rik RIKEN cDNA 9130404D08 gene | 1.7          | -1.6        | -1.4        |
|           | -           | 1.4          | 1.8         | 1.6         |
| 98667     | AW112037 expressed sequence AW112037 | 1.3          | 1.6         | 1.7         |
|           | -           |             |             |             |
| 98732     | 1110059F07Rik RIKEN cDNA 1110059F07 gene | 1.7          |             |             |
| 70273     | 2310051E17Rik RIKEN cDNA 2310051E17 gene | 1.7          |             |             |
| 217217    | Asb16 ankyrin repeat and SOCS box-containing 16 | 1.6          |             |             |
|           | -           |             |             |             |
| 75909     | 4930579A11Rik RIKEN cDNA 4930579A11 gene | 1.5          | 1.7         |             |
| 57443     | Fbxo3 F-box only protein 3 | -1.7         |             |             |
| Gene ID | Description | Expression 1 | Expression 2 |
|--------|-------------|-------------|-------------|
| 97282  | R75581      | 1.7         |             |
| 59308  | MGI:1891716 | 1.4         | 1.7         |
| 20610  | Sumo3       | -           | 1.6         |
| 74155  | 1300002F13Rik | 1.7       | 1.3         |
| 52331  | D5Ert593e   | -1.7        | -1.4        |
| 66627  | 5730405M13Rik | 1.5       |             |
| 66945  | Sdha        | -1.4        | -1.5        | -1.6 |
| 56374  | ORF18       | -           | 1.6         |
| 214489 | BC003965    | 1.4         | 1.5         |
| 71820  | Wdr34       | -           | 1.6         |
| 106522 | AW548124    | 1.6         |             |
| 15374  | Hn1         | -           | 1.6         |
| 56722  | Litaf       | -           | 1.5         |
| 66870  | 1200009K13Rik | -1.6     |             |
| 382038 | AK122209    | 1.6         |             |
| 235674 | MGC29978    | -1.6        |             |
| 320594 | 9130004C02Rik | 1.5       |             |
| 110172 | Ugal2       | 1.5         |             |
| 236520 | 9130229H14Rik | -1.5    |             |
| 66442  | 2600017H08Rik | 1.5       |             |
| 52822  | D5Bwg0860e  | -1.5        |             |
Table 2S. EASE Biological Theme Analysis

2 hour: Upregulated genes

| System                  | Category                                | EASE Score |
|-------------------------|-----------------------------------------|------------|
| molecular_function      | chymotrypsin activity                   | 0.000112   |
| molecular_function      | trypsin activity                        | 0.000302   |
| biological_process      | digestion                               | 0.000548   |
| molecular_function      | serine-type endopeptidase activity      | 0.000786   |
| molecular_function      | serine-type peptidase activity          | 0.00099    |
| cellular_component      | extracellular space                     | 0.00124    |
| cellular_component      | extracellular                           | 0.00166    |
| biological_process      | organismal physiological process        | 0.00195    |
| molecular_function      | catalytic activity                      | 0.00435    |
| biological_process      | catabolism                              | 0.0105     |
| biological_process      | amine catabolism                        | 0.0238     |
| molecular_function      | endopeptidase activity                  | 0.025      |
| cellular_component      | lytic vacuole                           | 0.0297     |
| cellular_component      | lysosome                                | 0.0297     |
| cellular_component      | vacuole                                 | 0.0397     |
| biological_process      | sulfur metabolism                       | 0.0429     |
| molecular_function      | peptidase activity                      | 0.0438     |
| molecular_function      | copper ion binding                      | 0.0481     |

2 hour: Downregulated genes

| System                  | Category                                | EASE Score |
|-------------------------|-----------------------------------------|------------|
| cellular_component      | cytoplasm                               | 0.000126   |
| cellular_component      | endoplasmic reticulum                   | 0.000205   |
| molecular_function      | oxidoreductase activity                 | 0.0003     |
| cellular_component      | peroxisome                              | 0.00204    |
| cellular_component      | microbody                               | 0.00204    |
| molecular_function      | glutathione transferase activity        | 0.0024     |
| biological_process      | hormone metabolism                      | 0.00242    |
| molecular_function      | monooxygenase activity                  | 0.00269    |
| cellular_component      | vesicular fraction                      | 0.00364    |
| cellular_component      | microsome                               | 0.00364    |
| biological_process      | response to abiotic stimulus            | 0.00532    |
| biological_process      | response to external stimulus           | 0.00697    |
| biological_process      | C21-steroid hormone biosynthesis        | 0.00785    |
| biological_process      | hormone biosynthesis                    | 0.00785    |
| molecular_function      | oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor | 0.00791    |
| biological_process      | steroid biosynthesis                    | 0.00913    |
| biological_process      | lipid metabolism                        | 0.0097     |
| biological_process      | C21-steroid hormone metabolism          | 0.0103     |
| molecular_function      | oxidoreductase activity, acting on CH-OH group of donors | 0.0108     |
| cellular_component | mitochondrion | 0.0122 |
|-------------------|--------------|--------|
| biological_process | fatty acid metabolism | 0.013 |
| cellular_component | intracellular | 0.0154 |
| molecular_function | catalytic activity | 0.0164 |
| molecular_function | transferase activity, transferring alkyl or aryl (other than methyl) groups | 0.0192 |
| biological_process | response to chemical substance | 0.0196 |
| cellular_component | membrane fraction | 0.0224 |
| biological_process | lipid biosynthesis | 0.0237 |
| biological_process | electron transport | 0.0269 |
| biological_process | steroid metabolism | 0.0299 |
| biological_process | physiological process | 0.0352 |
| cellular_component | cell fraction | 0.0405 |

**16h Upregulated genes**

| System | Category | EASE Score |
|--------|----------|------------|
| molecular_function | structural molecule activity | 1.17E-10 |
| molecular_function | structural constituent of ribosome | 1.47E-09 |
| cellular_component | ribosome | 1.91E-09 |
| biological_process | cytoplasm organization and biogenesis | 3.66E-09 |
| biological_process | protein biosynthesis | 3.72E-09 |
| cellular_component | ribonucleoprotein complex | 1.64E-08 |
| cellular_component | cytoplasm | 2.20E-08 |
| biological_process | macromolecule biosynthesis | 7.32E-08 |
| biological_process | biosynthesis | 0.00000129 |
| cellular_component | cytosolic ribosome (sensu Eukarya) | 0.00000201 |
| molecular_function | structural constituent of cytoskeleton | 0.00000438 |
| biological_process | ribosome biogenesis | 0.00000261 |
| biological_process | ribosome biogenesis and assembly | 0.0000329 |
| cellular_component | cytosol | 0.0000366 |
| biological_process | cell organization and biogenesis | 0.0000529 |
| cellular_component | cytoskeleton | 0.0000508 |
| biological_process | protein metabolism | 0.000093 |
| biological_process | cytoskeleton organization and biogenesis | 0.00026 |
| molecular_function | RNA binding | 0.000463 |
| biological_process | organelle organization and biogenesis | 0.000516 |
| cellular_component | eukaryotic 43S preinitiation complex | 0.000526 |
| cellular_component | small ribosomal subunit | 0.000732 |
| biological_process | cellular physiological process | 0.000804 |
| biological_process | cell growth and/or maintenance | 0.000907 |
| biological_process | microtubule-based process | 0.00141 |
| cellular_component | actin cytoskeleton | 0.00261 |
| cellular_component | cytosolic small ribosomal subunit (sensu Eukarya) | 0.00266 |
| cellular_component | eukaryotic 48S initiation complex | 0.00266 |
| biological_process | translation | 0.0028 |
| biological_process | protein targeting | 0.00555 |
| cellular_component | intracellular | 0.00609 |
|-------------------|---------------|---------|
| cellular_component | microtubule   | 0.00828 |
| biological_process| translational elongation | 0.00947 |
| cellular_component | microtubule cytoskeleton | 0.0119 |
| biological_process| intracellular transport | 0.0128 |
| biological_process| physiological process | 0.0129 |
| molecular_function | chaperone activity | 0.0147 |
| molecular_function | GTP binding | 0.0147 |
| molecular_function | guanyl nucleotide binding | 0.0147 |
| biological_process| pyrimidine ribonucleotide metabolism | 0.0167 |
| biological_process| pyrimidine ribonucleotide biosynthesis | 0.0167 |
| cellular_component | eukaryotic translation elongation factor 1 complex | 0.0249 |
| biological_process| protein folding | 0.029 |
| molecular_function | transferase activity, transferring acyl groups | 0.0296 |
| molecular_function | lipid binding | 0.0326 |
| biological_process| cation homeostasis | 0.0342 |
| biological_process| ion homeostasis | 0.0342 |
| biological_process| cell ion homeostasis | 0.0342 |
| molecular_function | binding | 0.0383 |
| molecular_function | translation factor activity, nucleic acid binding | 0.045 |
| cellular_component | intermediate filament cytoskeleton | 0.0487 |
| cellular_component | intermediate filament | 0.0487 |

### 16h Downregulated genes

| System                      | Category                                      | EASE Score  |
|-----------------------------|-----------------------------------------------|-------------|
| molecular_function          | oxidoreductase activity                       | 3.88E-15    |
| molecular_function          | catalytic activity                            | 2.02E-10    |
| biological_process          | organic acid metabolism                       | 7.38E-09    |
| biological_process          | carboxylic acid metabolism                    | 7.38E-09    |
| molecular_function          | lyase activity                                | 0.000000621 |
| biological_process          | aromatic compound metabolism                  | 0.00000209  |
| molecular_function          | hydro-lyase activity                          | 0.00000252  |
| biological_process          | steroid biosynthesis                          | 0.00000325  |
| molecular_function          | carbon-oxygen lyase activity                  | 0.00000359  |
| biological_process          | lipid metabolism                              | 0.00000363  |
| biological_process          | steroid metabolism                            | 0.00000774  |
| biological_process          | amino acid and derivative metabolism          | 0.0000214   |
| biological_process          | amine catabolism                              | 0.0000251   |
| biological_process          | sterol metabolism                             | 0.0000459   |
| biological_process          | lipid biosynthesis                            | 0.000047    |
| biological_process          | sterol biosynthesis                           | 0.0000486   |
| biological_process          | amine metabolism                              | 0.0000567   |
| biological_process          | amino acid catabolism                         | 0.0000711   |
| molecular_function          | glutathione transferase activity              | 0.0000759   |
| cellular_component          | peroxisome                                    | 0.000109    |
| cellular_component          | microbody                                     | 0.000109    |
| biological_process                  | amino acid metabolism                  | 0.000257 |
|------------------------------------|----------------------------------------|----------|
| biological_process                  | L-phenylalanine metabolism              | 0.000304 |
| biological_process                  | metabolism                             | 0.000338 |
| molecular_function                  | transferase activity, transferring alkyl or aryl (other than methyl) groups | 0.000386 |
| biological_process                  | alcohol metabolism                      | 0.000443 |
| biological_process                  | aromatic amino acid family metabolism   | 0.000593 |
| molecular_function                  | oxidoreductase activity, acting on CH-OH group of donors | 0.000674 |
| biological_process                  | hormone metabolism                      | 0.000773 |
| biological_process                  | electron transport                      | 0.000948 |
| biological_process                  | sulfur metabolism                       | 0.000973 |
| biological_process                  | fatty acid metabolism                   | 0.00308  |
| biological_process                  | cholesterol metabolism                  | 0.00323  |
| molecular_function                  | monooxygenase activity                  | 0.00327  |
| biological_process                  | coenzyme and prosthetic group metabolism| 0.00426  |
| biological_process                  | cholesterol biosynthesis                | 0.00567  |
| biological_process                  | aromatic amino acid family catabolism   | 0.00582  |
| biological_process                  | aromatic compound catabolism            | 0.00582  |
| biological_process                  | phenylalanine catabolism                | 0.00582  |
| biological_process                  | cysteine metabolism                     | 0.00582  |
| cellular_component                  | cytoplasm                              | 0.00743  |
| biological_process                  | heterocycle metabolism                  | 0.00745  |
| molecular_function                  | electron carrier activity               | 0.00927  |
| biological_process                  | amino acid derivative metabolism        | 0.00984  |
| biological_process                  | catabolism                             | 0.0114   |
| molecular_function                  | oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor | 0.0118   |
| biological_process                  | main pathways of carbohydrate metabolism| 0.0135  |
| cellular_component                  | mitochondrion                           | 0.0148   |
| cellular_component                  | cell fraction                           | 0.0189   |
| biological_process                  | C21-steroid hormone biosynthesis        | 0.0191   |
| biological_process                  | hormone biosynthesis                    | 0.0191   |
| molecular_function                  | carbonate dehydratase activity          | 0.0196   |
| cellular_component                  | extracellular space                     | 0.0198   |
| molecular_function                  | zinc ion binding                        | 0.0203   |
| cellular_component                  | extracellular                           | 0.0231   |
| biological_process                  | C21-steroid hormone metabolism          | 0.025    |
| biological_process                  | sulfur amino acid metabolism            | 0.025    |
| biological_process                  | isoprenoid metabolism                   | 0.025    |
| molecular_function                  | serine-type endopeptidase inhibitor activity | 0.0252  |
| molecular_function                  | carboxylic ester hydrolase activity     | 0.0303   |
| biological_process                  | serine family amino acid metabolism     | 0.0315   |
| biological_process                  | coenzyme metabolism                     | 0.0319   |
| biological_process                  | biosynthesis                            | 0.0351   |
| cellular_component                  | endoplasmic reticulum                   | 0.0353   |
| biological_process                  | detection of mechanical stimulus        | 0.0385   |
| biological_process                  | sensory perception of mechanical stimulus| 0.0385  |
| biological_process | perception of sound | 0.0385 |
|-------------------|---------------------|--------|
| biological_process | energy derivation by oxidation of organic compounds | 0.0388 |
| molecular_function | vitamin binding | 0.0394 |
| molecular_function | steroid binding | 0.0394 |
| biological_process | energy pathways | 0.0439 |
| biological_process | physiological process | 0.0465 |

### 40h Upregulated genes

| System                      | Category                                                                 | EASE Score |
|-----------------------------|--------------------------------------------------------------------------|------------|
| molecular_function          | structural constituent of ribosome                                       | 8.87E-18   |
| cellular_component          | ribosome                                                                 | 6.31E-17   |
| molecular_function          | structural molecule activity                                              | 2.62E-15   |
| cellular_component          | cytoplasm                                                                | 5.65E-13   |
| cellular_component          | cytosolic ribosome (sensu Eukarya)                                       | 1.66E-12   |
| biological_process          | protein biosynthesis                                                     | 3.18E-12   |
| cellular_component          | ribonucleoprotein complex                                                | 5.13E-12   |
| cellular_component          | cytosol                                                                  | 5.43E-11   |
| biological_process          | biosynthesis                                                             | 1.5E-10    |
| biological_process          | macromolecule biosynthesis                                               | 2.07E-10   |
| molecular_function          | structural constituent of cytoskeleton                                   | 2.17E-09   |
| biological_process          | physiological process                                                    | 9.85E-09   |
| biological_process          | protein metabolism                                                       | 9.91E-08   |
| biological_process          | ribosome biogenesis                                                      | 0.000000155|
| biological_process          | cytoplasm organization and biogenesis                                     | 0.000000241|
| biological_process          | ribosome biogenesis and assembly                                          | 0.000000247|
| biological_process          | cell organization and biogenesis                                          | 0.00000394 |
| cellular_component          | eukaryotic 43S preinitiation complex                                      | 0.0000068  |
| molecular_function          | RNA binding                                                              | 0.00000754 |
| cellular_component          | cytoskeleton                                                              | 0.0000105  |
| cellular_component          | actin cytoskeleton                                                       | 0.0000113  |
| biological_process          | cellular physiological process                                            | 0.0000176  |
| biological_process          | cell growth and/or maintenance                                           | 0.0000196  |
| cellular_component          | intracellular                                                            | 0.0000872  |
| cellular_component          | cytosolic small ribosomal subunit (sensu Eukarya)                         | 0.000131   |
| cellular_component          | eukaryotic 48S initiation complex                                         | 0.000131   |
| cellular_component          | small ribosomal subunit                                                  | 0.000254   |
| cellular_component          | Arp2/3 protein complex                                                    | 0.000388   |
| biological_process          | protein folding                                                          | 0.00107    |
| biological_process          | cytoskeleton organization and biogenesis                                  | 0.00182    |
| biological_process          | digestion                                                                | 0.00254    |
| biological_process          | translation                                                              | 0.00309    |
| molecular_function          | isomerase activity                                                       | 0.00389    |
| biological_process          | metabolism                                                               | 0.0055     |
| molecular_function          | translation factor activity, nucleic acid binding                         | 0.00647    |
| molecular_function | lipid binding | 0.00716 |
|-------------------|--------------|---------|
| biological_process | organelle organization and biogenesis | 0.00824 |
| biological_process | translational elongation | 0.0107 |
| molecular_function | translation regulator activity | 0.011 |
| biological_process | nucleoside triphosphate biosynthesis | 0.0125 |
| cellular_component | proteasome complex (sensu Eukarya) | 0.0136 |
| cellular_component | striated muscle thin filament | 0.0153 |
| biological_process | ribonucleotide biosynthesis | 0.0164 |
| biological_process | purine ribonucleoside triphosphate biosynthesis | 0.0165 |
| biological_process | ribonucleoside triphosphate biosynthesis | 0.0165 |
| biological_process | purine nucleoside triphosphate biosynthesis | 0.0165 |
| biological_process | nucleoside triphosphate metabolism | 0.0167 |
| cellular_component | microtubule cytoskeleton | 0.018 |
| biological_process | protein targeting | 0.0194 |
| molecular_function | translation initiation factor activity | 0.0212 |
| biological_process | purine ribonucleoside triphosphate metabolism | 0.0222 |
| biological_process | ribonucleoside triphosphate metabolism | 0.0222 |
| biological_process | purine nucleoside triphosphate metabolism | 0.0222 |
| biological_process | intracellular transport | 0.0253 |
| molecular_function | ATPase activity, coupled to transmembrane movement of ions | 0.0258 |
| molecular_function | ATPase activity, coupled to transmembrane movement of ions, phosphorylative mechanism | 0.0258 |
| biological_process | proton transport | 0.028 |
| biological_process | ribonucleotide metabolism | 0.0329 |
| biological_process | microtubule-based process | 0.0337 |
| cellular_component | proteasome core complex (sensu Eukarya) | 0.0343 |
| cellular_component | intermediate filament | 0.0343 |
| cellular_component | intermediate filament cytoskeleton | 0.0343 |
| cellular_component | microtubule | 0.0343 |
| cellular_component | cell | 0.0361 |
| cellular_component | nuclear membrane | 0.0364 |
| biological_process | DNA packaging | 0.0387 |
| molecular_function | hydrogen-exporting ATPase activity, phosphorylative mechanism | 0.042 |

### 40h Downregulated genes

| System | Category | EASE Score |
|--------|----------|------------|
| molecular_function | oxidoreductase activity | 3.88E-11 |
| molecular_function | catalytic activity | 2.32E-08 |
| cellular_component | peroxisome | 7.14E-08 |
| cellular_component | microbody | 7.14E-08 |
| biological_process | carboxylic acid metabolism | 0.00000021 |
| biological_process | organic acid metabolism | 0.00000021 |
| biological_process                  | lipid metabolism             | 0.00000321 |
|------------------------------------|------------------------------|------------|
| cellular_component                 | cytoplasm                    | 0.00000352 |
| biological_process                 | steroid biosynthesis         | 0.00000437 |
| biological_process                 | steroid metabolism           | 0.00000706 |
| biological_process                 | fatty acid metabolism        | 0.00000758 |
| molecular_function                 | lyase activity               | 0.000133   |
| biological_process                 | aromatic compound metabolism | 0.000232   |
| biological_process                 | lipid biosynthesis           | 0.000279   |
| molecular_function                 | oxidoreductase activity, acting on CH-OH group of donors, NAD or NADP as acceptor | 0.000303 |
| molecular_function                 | hydro-lyase activity         | 0.000368   |
| molecular_function                 | monooxygenase activity       | 0.000376   |
| molecular_function                 | carbon-oxygen lyase activity | 0.000464   |
| biological_process                 | sterol metabolism            | 0.0005     |
| molecular_function                 | oxidoreductase activity, acting on CH-OH group of donors | 0.000534 |
| biological_process                 | sterol biosynthesis          | 0.000748   |
| biological_process                 | alcohol metabolism           | 0.00191    |
| cellular_component                 | endoplasmic reticulum        | 0.00328    |
| biological_process                 | coenzyme and prosthetic group metabolism | 0.00406 |
| cellular_component                 | mitochondrion                | 0.0046     |
| biological_process                 | coenzyme metabolism          | 0.00791    |
| biological_process                 | hormone metabolism           | 0.00874    |
| biological_process                 | energy derivation by oxidation of organic compounds | 0.0102 |
| biological_process                 | metabolism                   | 0.0102     |
| biological_process                 | energy pathways              | 0.0119     |
| biological_process                 | main pathways of carbohydrate metabolism | 0.013 |
| molecular_function                 | zinc ion binding             | 0.0168     |
| molecular_function                 | carbonate dehydratase activity | 0.0182 |
| biological_process                 | C21-steroid hormone biosynthesis | 0.0188 |
| biological_process                 | hormone biosynthesis         | 0.0188     |
| biological_process                 | cholesterol metabolism       | 0.0238     |
| biological_process                 | C21-steroid hormone metabolism | 0.0246 |
| molecular_function                 | transition metal ion binding | 0.0247     |
| cellular_component                 | cell fraction                | 0.0254     |
| biological_process                 | carbohydrate metabolism      | 0.0256     |
| molecular_function                 | carboxylic ester hydrolase activity | 0.0267 |
| cellular_component                 | integral to membrane         | 0.0351     |
| biological_process                 | peroxisome organization and biogenesis | 0.0379 |
| biological_process                 | heterocycle metabolism       | 0.0429     |
| biological_process                 | sulfur metabolism            | 0.0429     |