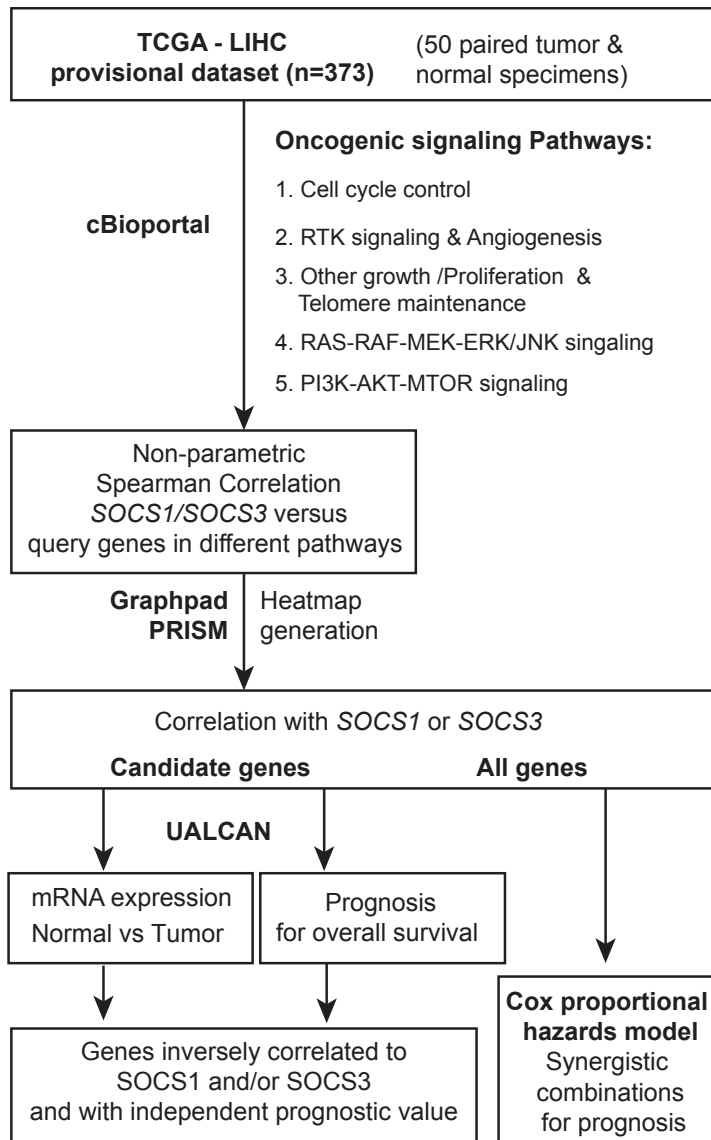
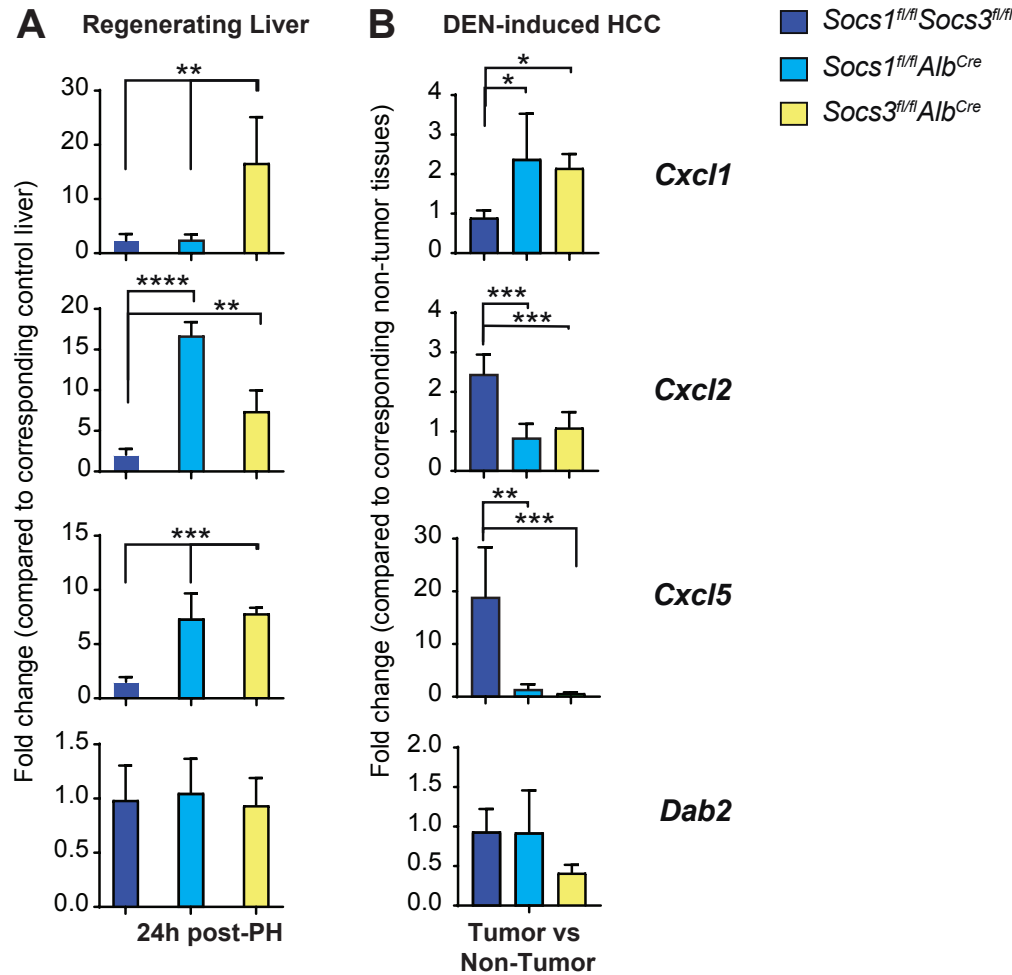




**Figure S1. Workflow of this study.**



**Figure S2. Expression of oncogenic signaling pathway genes that synergize with *SOCS1* or *SOCS3* in predicting prognosis by the Cox proportional hazards model in the murine models.** *DAB2* and *CXCL8* synergize with *SOCS1* or *SOCS3* in predicting prognosis by the Cox proportional hazards model (shown in Table 2). As the *CXCL8* (IL-8) gene is not present in the mouse, we examined the genes coding for mouse chemokines KC (*Cxcl1*), MIP-2 (*Cxcl2*) and LIX (*Cxcl2*), which are considered the functional equivalent of human *CXCL8* in promoting neutrophil migration. (A) Partial hepatectomy was carried out on 8-10 weeks old mice lacking *Socs1* or *Socs3* in hepatocytes and control mice. The expression of the indicated genes in the regenerating livers was evaluated 24h later by qRT-PCR. n=4-6 mice per group. (B) Mice lacking *Socs1* or *Socs3* in hepatocytes and control mice were treated with DEN (25 mg/kg body weight) at 2 weeks of age and livers collected at 8-10 months of age. Tumor nodules and adjacent normal liver tissues were resected and expression of the indicated genes was evaluated by qRT-PCR. n=4-6 mice per group. p-values were calculated by one-way ANOVA along with Tukey's Multiple Comparison test: \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001, \*\*\*\* p < 0.0001.

**Supplementary Table S1:** List of qRT-PCR primers used in this study.

| Gene name           | Gene ID      | Sense primer               | Anti-sense primer        | Amplicon Size (bp) |
|---------------------|--------------|----------------------------|--------------------------|--------------------|
| <i>Aurka</i>        | NM_011497    | TGAGTTGGAAAGGGACATGG       | GGACCCCTCTGCATTGATAAG    | 136                |
| <i>Cdk2</i>         | NM_016756    | GCATTCCCTCTTCCCCTCATC      | GGACCCCTCTGCATTGATAAG    | 128                |
| <i>Mist8</i>        | NM_019988    | CTGAGTCTTCCATCACGTCTG      | GATCTTGGTCTTAGGGATGAGC   | 143                |
| <i>Rptor</i>        | NM_028898    | CACTCCTTGTCTTCATCTGGG      | TGTCATGGTCCTATGTTTCAGC   | 140                |
| <i>Map3k4</i>       | NM_011948    | ATGTTGGACTGAGGAAGGTG       | TGGTCGTTAGGCTGAAATCG     | 145                |
| <i>36B4 (Rplp0)</i> | NM_007475.5  | TCTGGAGGGTGTCCGCAA         | CTTGACCTTTTCAGTAAGTGG    | 154                |
| <i>Dab2</i>         | NM_001037905 | AGCCAGTCTTTTGCTCATCTG      | TCCAAAGGGTTCAGCTCATC     | 140                |
| <i>Cxcl1</i>        | NM_008176.3  | AACCGAAGTCATAGCCACAC       | CAGACGGTGCCATCAGAG       | 147                |
| <i>Cxcl2</i>        | NM_009140.2  | AAAATCATCCAAAAGATACTGAACAA | CTTTGGTTCTTCCGTTGAGG     | 91                 |
| <i>Cxcl5</i>        | NM_009141.3  | GGGAAACCATTGTCCTGA         | TCCGATAGTGTGACAGATAGGAAA | 92                 |

**Supplementary Table S2.** Impact of the expression of oncogenic pathway genes on survival probability in the TCGA-LIHC dataset.

| Oncogenic signaling pathway  | Gene Name*    | High exp. (n) | Low/Med. Exp (n) | Survival probability p-value | Expression Level for poor prognosis |
|------------------------------|---------------|---------------|------------------|------------------------------|-------------------------------------|
| Cell Cycle                   | <i>STAT5B</i> | 92            | 273              | 0.96                         |                                     |
|                              | <i>CDK6</i>   | 90            | 275              | 0.22                         |                                     |
|                              | <i>RBL2</i>   | 93            | 272              | 0.76                         |                                     |
|                              | <i>CDK2</i>   | 90            | 275              | <b>0.011</b>                 | High                                |
|                              | <i>CCND1</i>  | 90            | 275              | 0.95                         |                                     |
|                              | <i>CDKN1B</i> | 92            | 273              | 0.18                         |                                     |
|                              | <i>RB1</i>    | 90            | 275              | 0.077                        |                                     |
|                              | <i>RBL1</i>   | 91            | 274              | <b>0.044</b>                 | High                                |
|                              | <i>E2F7</i>   | 92            | 273              | <b>0.0044</b>                | High                                |
|                              | <i>E2F8</i>   | 91            | 274              | <b>0.006</b>                 | High                                |
|                              | <i>JAK1</i>   | 91            | 274              | 0.17                         |                                     |
|                              | <i>E2F6</i>   | 89            | 276              | <b>0.00021</b>               | High                                |
|                              | <i>MYC</i>    | 91            | 274              | 0.32                         |                                     |
|                              | <i>E2F1</i>   | 92            | 273              | 0.1                          |                                     |
|                              | <i>CDK1</i>   | 89            | 276              | <b>&lt;0.0001</b>            | High                                |
|                              | <i>CDC25A</i> | 89            | 276              | <b>&lt;0.0001</b>            | High                                |
|                              | <i>CDKN2B</i> | 91            | 274              | <b>0.0016</b>                | High                                |
|                              | <i>E2F5</i>   | 89            | 276              | <b>0.0021</b>                | High                                |
|                              | <i>CCNB1</i>  | 90            | 275              | <b>&lt;0.0001</b>            | High                                |
|                              | <i>CDK4</i>   | 88            | 277              | <b>&lt;0.0001</b>            | High                                |
|                              | <i>SRC</i>    | 92            | 273              | <b>0.00049</b>               | High                                |
|                              | <i>CDKN2A</i> | 91            | 274              | <b>0.014</b>                 | High                                |
|                              | <i>STAT2</i>  | 91            | 274              | 0.49                         |                                     |
|                              | <i>CCNA1</i>  | 92            | 273              | 0.33                         |                                     |
|                              | <i>E2F3</i>   | 89            | 276              | 0.13                         |                                     |
|                              | <i>E2F2</i>   | 90            | 275              | 0.096                        |                                     |
|                              | <i>E2F4</i>   | 88            | 277              | <b>0.00019</b>               | High                                |
|                              | <i>CCNE1</i>  | 92            | 273              | <b>0.00077</b>               | High                                |
|                              | <i>STAT1</i>  | 91            | 274              | 0.16                         |                                     |
|                              | <i>CDKN1A</i> | 91            | 274              | 0.75                         |                                     |
|                              | <i>JAK2</i>   | 90            | 275              | 0.91                         |                                     |
|                              | <i>STAT5A</i> | 91            | 274              | 0.75                         |                                     |
|                              | <i>STAT3</i>  | 92            | 273              | 0.42                         |                                     |
|                              | <i>CCND2</i>  | 90            | 275              | 0.66                         |                                     |
| RTK signaling & Angiogenesis | <i>MET</i>    | 93            | 272              | 0.64                         |                                     |
|                              | <i>ERBB2</i>  | 93            | 272              | 0.34                         |                                     |
|                              | <i>KDR</i>    | 93            | 272              | 0.088                        |                                     |
|                              | <i>EGFR</i>   | 93            | 272              | 0.54                         |                                     |
|                              | <i>VEGFA</i>  | 90            | 275              | <b>&lt;0.0001</b>            | High                                |
|                              | <i>KIT</i>    | 91            | 274              | 0.093                        |                                     |
|                              | <i>PDGFB</i>  | 92            | 273              | 0.96                         |                                     |
|                              | <i>IGF1</i>   | 93            | 272              | 0.089                        |                                     |

|                                      |                      |    |     |                   |      |
|--------------------------------------|----------------------|----|-----|-------------------|------|
|                                      | <i>PDGFRB</i>        | 92 | 273 | 0.35              |      |
|                                      | <i>ERBB4</i>         | 92 | 273 | 0.67              |      |
|                                      | <b><i>ERBB3</i></b>  | 92 | 273 | <b>0.0081</b>     | High |
|                                      | <i>PDGFA</i>         | 92 | 273 | 0.62              |      |
|                                      | <i>FGF1</i>          | 92 | 273 | 0.46              |      |
|                                      | <i>IGF1R</i>         | 89 | 276 | 0.29              |      |
|                                      | <i>FGFR1</i>         | 92 | 273 | 0.44              |      |
|                                      | <i>PDGFRA</i>        | 91 | 274 | 0.24              |      |
|                                      | <i>VEGFB</i>         | 91 | 274 | 0.61              |      |
|                                      | <i>CXCR1</i>         | 91 | 274 | 0.52              |      |
|                                      | <i>CXCR2</i>         | 91 | 274 | 0.96              |      |
|                                      | <b><i>CXCL8</i></b>  | 92 | 273 | <b>0.01</b>       | High |
| <hr/>                                |                      |    |     |                   |      |
| Other growth &<br>Proliferation/TERT | <i>DPH1</i>          | 92 | 273 | 0.67              |      |
|                                      | <i>DLEC1</i>         | 92 | 273 | 0.24              |      |
|                                      | <b><i>AURKA</i></b>  | 90 | 275 | <b>0.0016</b>     | High |
|                                      | <i>IGF1</i>          | 93 | 272 | 0.089             |      |
|                                      | <i>OPCML</i>         | 92 | 273 | 0.7               |      |
|                                      | <i>FGF1</i>          | 92 | 273 | 0.46              |      |
|                                      | <i>PLAGL1</i>        | 89 | 276 | 0.74              |      |
|                                      | <i>IGF1R</i>         | 89 | 276 | 0.29              |      |
|                                      | <i>FGFR1</i>         | 92 | 273 | 0.44              |      |
|                                      | <b><i>CSF1</i></b>   | 91 | 274 | <b>&lt;0.0001</b> | High |
|                                      | <i>CSF1R</i>         | 90 | 275 | 0.15              |      |
|                                      | <i>TERT</i>          | 91 | 274 | 0.51              |      |
|                                      | <i>TERC</i>          | 92 | 273 | 0.31              |      |
| <hr/>                                |                      |    |     |                   |      |
| RAS-RAF-MEK-<br>ERK/JNK              | <b><i>MAPK1</i></b>  | 91 | 274 | <b>0.013</b>      | High |
|                                      | <i>MAPK8</i>         | 93 | 272 | 0.13              |      |
|                                      | <i>MAPK14</i>        | 91 | 274 | 0.19              |      |
|                                      | <i>MAPK6</i>         | 90 | 275 | 0.14              |      |
|                                      | <i>MAP2K5</i>        | 92 | 273 | 0.93              |      |
|                                      | <b><i>BRAF</i></b>   | 92 | 273 | <b>0.0066</b>     | High |
|                                      | <i>RAF1</i>          | 91 | 274 | 0.17              |      |
|                                      | <i>MAP3K2</i>        | 93 | 272 | 0.81              |      |
|                                      | <b><i>MAP3K4</i></b> | 89 | 276 | <b>0.0025</b>     | High |
|                                      | <i>KRAS</i>          | 93 | 272 | 0.11              |      |
|                                      | <i>MAP2K4</i>        | 92 | 273 | 0.51              |      |
|                                      | <i>MAP3K1</i>        | 90 | 275 | 0.28              |      |
|                                      | <i>MAPK9</i>         | 90 | 275 | 0.21              |      |
|                                      | <i>MAPK4</i>         | 93 | 272 | 0.56              |      |
|                                      | <i>MAP3K3</i>        | 92 | 273 | 0.14              |      |
|                                      | <i>MAP2K1</i>        | 91 | 274 | 0.28              |      |
|                                      | <i>MAP2K3</i>        | 91 | 274 | 0.22              |      |
|                                      | <b><i>MAPK7</i></b>  | 91 | 274 | <b>0.0061</b>     | High |
|                                      | <b><i>MAP2K2</i></b> | 90 | 275 | <b>0.0034</b>     | High |
|                                      | <i>RAB25</i>         | 93 | 272 | 0.51              |      |
|                                      | <b><i>MAPK12</i></b> | 92 | 273 | <b>0.026</b>      | High |
|                                      | <b><i>MAPK3</i></b>  | 92 | 273 | <b>0.00015</b>    | High |

|                      |               |    |     |                |      |
|----------------------|---------------|----|-----|----------------|------|
|                      | <b>HRAS</b>   | 88 | 277 | <b>0.00073</b> | High |
|                      | <b>RASSF1</b> | 89 | 276 | <b>0.013</b>   | High |
|                      | <b>MAP3K5</b> | 92 | 273 | 0.54           |      |
|                      | <b>DAB2</b>   | 92 | 273 | <b>0.00046</b> | High |
| <b>PI3K-AKT-MTOR</b> | <b>PIK3R1</b> | 93 | 272 | <b>0.012</b>   | Low  |
|                      | <b>PDPK1</b>  | 93 | 272 | 0.25           |      |
|                      | <b>RPTOR</b>  | 90 | 275 | <b>0.0043</b>  | High |
|                      | <b>PTEN</b>   | 91 | 274 | 0.47           |      |
|                      | <b>AKT2</b>   | 92 | 273 | 0.38           |      |
|                      | <b>PIK3CA</b> | 93 | 272 | <b>0.0088</b>  | High |
|                      | <b>MTOR</b>   | 93 | 272 | 0.18           |      |
|                      | <b>TSC1</b>   | 90 | 275 | <b>0.0028</b>  | High |
|                      | <b>TSC2</b>   | 92 | 273 | 0.2            |      |
|                      | <b>FOXO1</b>  | 93 | 272 | <b>0.027</b>   | Low  |
|                      | <b>RICTOR</b> | 92 | 273 | <b>0.0068</b>  | High |
|                      | <b>FOXO3</b>  | 91 | 274 | <b>0.0083</b>  | High |
|                      | <b>RHEB</b>   | 92 | 273 | <b>0.0026</b>  | High |
|                      | <b>PIK3R2</b> | 89 | 276 | <b>0.018</b>   | High |
|                      | <b>MLST8</b>  | 89 | 276 | <b>0.0014</b>  | High |
|                      | <b>AKT1S1</b> | 91 | 274 | <b>0.00073</b> | High |
|                      | <b>AKT1</b>   | 90 | 275 | <b>0.0015</b>  | High |

\* Gene names in **boldface**: Significant correlation with *SOCS1* (vary with *SOCS3*; see figures 3 to 6). Color codes:

**Green**: negative correlation (mutual exclusivity) with *SOCS1* or *SOCS3*.

**Black**: no correlation with *SOCS1*.

**Red**: positive correlation (co-occurrence) with *SOCS1*.

**Orange**: Prognosis discordant from expected functions.

**Supplementary Table S3.** Combinations of high *SOCS1* or high *SOCS3* and oncogenic signalling pathway genes that show significant prognosis in the Cox proportional hazard model.

| Selected Combinations                  | Oncogenic signaling Pathway  | Multivariate Cox model p-value | Univariate log-rank p-value | Survival probability | Number of subjects | HR [95% confidence intervals] |
|----------------------------------------|------------------------------|--------------------------------|-----------------------------|----------------------|--------------------|-------------------------------|
| High <i>SOCS1</i> + low <i>E2F5</i>    | Cell cycle                   | 0.0051                         | 0.0051                      | Better               | 22                 | 0.07 [0.01 - 0.05]            |
| High <i>SOCS1</i> + High <i>PDGFA</i>  | RTK signalling, angiogenesis | 0.0241                         | 0.0323                      | Better               | 26                 | 0.23 [0.09 - 0.61]            |
| High <i>SOCS1</i> + High <i>KDR</i>    | RTK signalling, angiogenesis | 0.0219                         | 0.0414                      | Better               | 19                 | 0.28 [0.09 - 0.89]            |
| High <i>SOCS1</i> + High <i>E2F7</i>   | Cell cycle                   | 0.0012                         | 0.0334                      | Poor                 | 21                 | 4.98 [2.29 - 10.84]           |
| High <i>SOCS1</i> + Low <i>OPCML</i>   | Proliferation                | 0.0304                         | 0.0483                      | Poor                 | 23                 | 2.45 [1.34 - 4.49]            |
| High <i>SOCS3</i> + High <i>STAT5B</i> | Cell cycle                   | 0.008                          | 0.0156                      | Better               | 15                 | 0.11 [0.02 - 0.79]            |
| High <i>SOCS3</i> + Low <i>PDGFB</i>   | RTK signalling, angiogenesis | 0.0394                         | 0.0317                      | Better               | 13                 | 0.16 [0.02 - 1.17]            |
| High <i>SOCS3</i> + High <i>FOXO1</i>  | PI3K-AKT pathway             | 0.0214                         | 0.0248                      | Better               | 34                 | 0.42 [0.2 - 0.92]             |
| High <i>SOCS3</i> + High <i>CDK1</i>   | Cell cycle                   | 0.0001                         | 0.0001                      | Poor                 | 19                 | 4.05 [2.15 - 7.63]            |
| High <i>SOCS3</i> + High <i>AURKA</i>  | Proliferation                | 0.0109                         | 0.0109                      | Poor                 | 20                 | 2.48 [1.29 - 4.77]            |
| High <i>SOCS3</i> + Low <i>MAP2K4</i>  | MAPK pathway                 | 0.0102                         | 0.0143                      | Poor                 | 16                 | 2.65 [1.41 - 4.96]            |

**Limitations:** Comparison of the top or bottom 25% (high or low) with the rest (75) is arbitrary. Some combination groups have only a very few number of cases (Total n=362).

**Color codes for high/low expression of individual genes:** Red: Poor prognosis; Green: Good prognosis; Blue: No prognostic value. \*, \*\* synergy with both low *SOCS1* and low *SOCS3*.