**CTGF**-positive cell number has the highest correlation of non-RNA factors with cluster 4 and shows continuous increase after BDL (Figure 3F). CTGF is the best candidate from those selected to monitor the disease progress. It is also among the parameters with the highest ANOVA significance (padj=7.9E-10). This is consistent with data from other studies, which observed a correlation of increased CTGF levels with histological fibrosis stages [62; 63], suggesting CTGF as a valuable diagnostic target, since it can be measured in patients’ blood and maybe used to follow-up on patients suffering from chronic liver diseases [64].

**Cyp1a2**

Transcript levels of genes involved in metabolism (ADME, Cluster ?) such as members of the cytochrome P450 system are immediately induced during the first 6 h upon damage and then steadily decrease with time after BDL. This time course suggests that early after the insult the detoxification activity of hepatocytes is increased but than decreases owing to ongoing necrosis of hepatocytes and feedback inhibition of CYP 450 expression by accumulating bile salts.

**Sparc**

Sparc (secreted acidic cysteine rich glycoprotein), a known indicator of chronic liver disease [53] and a mediator of fibrosis [61], also has a large separation gap.

**Cebpb**, which encodes CCAAT/enhancer-binding protein β, a regulator of the inflammatory response, e.g. via up-regulating Il6 [18].

**Cxcl1 & Cxcl2**

The two chemokines **Cxcl1**, encoding neutrophil-activating protein 3, and **Cxcl2**, encoding macrophage inflammatory protein 2-α. As both proteins are excreted, it is likely that they can be detected in the plasma and thus may be further investigated as potential diagnostic marker.

**Gstm1** (glutathione-S-transferase mu 1, Figure 6C) polymorphisms are a risk factor in alcoholic liver cirrhosis [67].

**Hmox1**

The second highest correlated factor to ALT is **Hmox1**, encoding heme oxygenase, which was reported as increased upon BDL [17]. It therefore also can be defined as “early response” parameter, which subsequently remains at increased levels as compared to healthy liver.

**Ccr5**, encoding C-C chemokine receptor type 5, which is a regulator of inflammation as well as macrophage recruitment and trafficking [49], thus representing a general promoter of hepatic fibrosis [50].

**Tnfrsf1a**, encoding isoform 1 of the receptor (see Figure 6L). The latter was previously reported as necessary for liver fibrosis in mice [51].

Then **Cxcr1**, encoding interleukin 8 receptor α, is reported to be highly up-regulated in chronic liver disease [52].

**Il17a** (interleukin-17A) (Figure 6H), plays a pivotal role in cholestatic liver fibrosis in mice by activation of both the KCs and HSCs [19]. Il17a is switched on between 2d and 5d to very high RNA levels, and as it is a secreted protein, it is likely to be detectable in the blood, thus representing a candidate diagnostic marker.

**Il28b** (interleukin 28β, see Figure 6K) polymorphisms are associated with fibrosis progression in patients with chronic hepatitis C [68].

**Il10rb** ( interleukin 10 receptor β subunit), which was found up-regulated in NASH with fibrosis [25]. **Il10rb**, encoding the β-subunit for the Il10 receptor, which was described to be increased in rat liver fibrosis [31].

Expression of **Notch3** is initially negatively and later positively correlated with bile infarcts. This corresponds to the pattern of Notch3 expression. It drops below the level of untreated mice and is increased between days 2 and 5. Notch3 is reported to be significantly up-regulated in fibrotic liver tissues, most supposedly by regulating the activation of HSCs [20].

**Prom1**, encoding prominin 1 (CD133), is reported to be increased in alcoholic hepatitis [21] and chronic liver injury [22], and was dedicated to be regulated by the DNA methylation in HSCs [23].

The factor **Por** (cytochrome P450 reductase) is reported to be down-regulated in liver cirrhosis via the aryl hydrocarbon receptor AhR [27].

**Col1a1** (Figure 6E), encoding the collagen deposited in ECM in large quantities

**Pparg** (peroxisome proliferator-activated receptor gamma), PPAR-γ inhibits HSC activation [42]. As Pparg is increasing only in the early stages, we conclude that TGF-β and Pparg form a threshold system, where HSC activation is controlled in the first stage and overshooting in later time frames.

**Notch1**, a transmembrane receptor involved in developmental processes, and its increase can as well be seen as a sign of cell plasticity and tissue restructuring.

**Gsta2**, encoding glutathione S-transferase A2 (Figure 9A), which facilitates bilirubin import [26].

**S100a4**-positive cells is a similarly good marker for disease progression, also among the top correlations of cluster 4, and similar time course than CTGF (Figure 3B), but larger variation than CTGF from 18h on.

**Tgfb**, encoding the cytokine TGFβ, which is well known to correspond with the fibrotic process in a positive feedback loop [30].

**Tnfrsf1a**

Tnfrsf1a (tumor necrosis factor 1, Figure 6L) aggravates steatohepatitis [65] and is essential for HSC proliferation and ECM remodeling [66].

**Cdh2**, encoding cadherin-2, which is normally associated to cancerous cells.

**Lama1**, encoding laminin subunit α-1. Lama1 was found to be increased in nonalcoholic fatty liver disease [29].

**Timp2**, encoding tissue inhibitor of metalloproteinases 2, an antagonist for degradation of extracellular matrix (ECM), also correlates with the hepatocyte proliferative response and reflects increased ECM deposition and buildup of fibrotic tissue.

**Ugt1a1**, encoding UDP-glucuronosyl-transferase 1A, the main enzyme for conjugation of bilirubin, whose down-regulation is considered protective against the increased concentration of conjugated bilirubin in hepatocytes.