Letter in response to 'Coagulation and fibrosis in chronic liver disease'
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LETTERS

The contribution of megakaryocytes to liver fibrosis

In a recent paper in Gut, Calvaruso et al1 give a succinct summary of the coagulation changes which predispose to fibrosis in chronic liver disease. However, they did not mention the important contribution of the megakaryocyte, in addition to thrombin, to liver fibrosis. This is exemplified by the observation of frequently fatal, liver fibrosis which can occur in acute megakaryoblastic leukaemia (AMKL) and transient myeloproliferative disorder (a precursor of AMKL) in children with Down syndrome.2 These children demonstrate sinusoidal fibrosis and extrahepatic haematoipoiesis in the liver, raising the possibility that the fibrosis is caused by cytokines elaborated by the liver megakaryocytes.3 Abnormal megakaryocytic progenitor cells which proliferate in the foetal liver, release cytokines, including platelet derived and transforming growth factors, potent stimulators of growth and collagen synthesis in fibroblasts, leading to liver fibrosis.4 Although in this context, a case against the presence of megakaryocytes in the adult liver may be made, it is important to note that extrahepatic haematoipoiesis has been demonstrated in the liver in many hematological disorders including haemoglobinopathies and storage disorders like Gaucher’s disease. In the non-haematological conditions, however, the elaboration of the fibrogenic cytokines from the bone marrow megakaryocytes can occur in the presence of thrombin.

Thrombin, the key molecule in the coagulation system, can stimulate megakaryocytes to release fibrogenic mediators including basic fibroblast, and vascular endothelial growth factors (VEGF).5 Both these growth factors are released physiologically, to help in sustaining haematopoietic colony growth in the presence of other cytokines.6 In instances of vascular injury, VEGF, in particular, can help in endothelial proliferation and angiogenesis as a part of wound healing, an exaggerated form of angiogenesis.6 Endothelial growth factors (VEGFs), in particular, can help in endothelial proliferation and angiogenesis as a part of wound healing, an exaggerated form of angiogenesis.6 Endothelial growth factors (VEGFs), in particular, can help in endothelial proliferation and angiogenesis as a part of wound healing, an exaggerated form of angiogenesis.6 VEGF and platelet derived growth factor (PDGF) are known to be mitogenic for fibroblasts.8 These characteristics have been exploited in conjunction with the other coagulation factors to further improve our understanding of liver fibrosis.

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Letter in response to ‘Coagulation and fibrosis in chronic liver disease’

We read with interest the paper by Calvaruso and colleagues discussing the role of coagulation in fibrosis in chronic liver disease. Fibrotic diseases, and especially liver fibrosis, are a major public health issue, and remain too often refractory to therapy. Novel treatment options are therefore eagerly awaited. Overall, we agree with the author’s conclusions that compelling evidence supports a close relationship between thrombin and hepatic fibrogenesis and that targeting the coagulation cascade might be an attractive therapeutic avenue for the management of liver fibrosis. This notion is underscored by the fact that anticoagulant therapy already showed promise in idiopathic pulmonary fibrosis where it improved overall survival.5

Although we would like to commend the authors on writing a valuable review on this highly relevant topic, we do feel they might have focused too much on the role of thrombin. The realisation that both coagulation and PAR-2 are instrumental in fibrogenesis boosted research on factor (F)Xa–PAR-2 driven signal transduction in pathophysiology. These recent experiments challenged the concept that FXa-induced signal transduction is simply reminiscent of thrombin-induced signal transduction.6

Calvaruso and colleagues briefly mention FXa by stating that similarly to thrombin, FXa acts as a potent mitogen on fibroblasts. Rather surprisingly, they state that the mitogenic effect might be mediated by the effectors proteinase receptor-1 (EPR-1). This is surprising because the existence of EPR-1 is highly controversial.4 Indeed, the cDNA encoding an inhibitor of apoptosis, survivin, is reportedly identical to that of EPR-1 except for a few nucleotide differences and with its orientation opposite to EPR-1. The published EPR-1 cDNA sequence is consequently believed to be derived from survivin mRNA. Most probably, therefore, FXa exerts its effects in fibrogenesis via PAR-2 activation.3

Interestingly, the authors of the recent review already suggest that (next to thrombin–PAR-1) PAR-2 activation might also contribute to liver fibrosis. This notion is based on the facts that PAR-2 expression is upregulated in livers of bile duct-ligated rats, that hepatic stellate cells (HSCs) express PAR-2 and that PAR-2 activation induced myofibroblast differentiation, cell proliferation, and collagen synthesis by HSCs. It is hypothesised that PAR-2 activation is elicited by mast cell tryptase. Although this is a likely candidate to activate PAR-2, we feel the potential role of FXa should not have been overlooked. The mitogenic effects of FXa in fibroblasts and smooth muscle cells of different tissues are well known.7 In addition, we recently showed that FXa induces fibroblast migration, extracellular matrix synthesis, transforming growth factor β release and fibroblast differentiation into myofibroblasts. All these fibroproliferative responses were mediated by PAR-2 activation, thereby at least suggesting that the FXa–PAR-2 axis acts as an important modifier in fibrotic disease.8

Overall the role of thrombin in liver fibrosis is indeed compelling, but the potential importance of FXa, which has already
been shown to be important in animal models of glomerulonephritis, restenosis, asthma and fibrosarcoma, might be as important. From a clinical perspective, one might even argue that FXa is a more attractive therapeutic target for liver fibrosis than thrombin. This notion is not only based on the fact that FXa inhibitors are more effective at lower doses than thrombin inhibitors but also on the fact that FXa inhibitors block both FXa-dependent profibrotic signalling and thrombin generation.

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REFERENCES


Applicability of BARD score to Japanese patients with NAFLD

We read the article by Harrison et al. with great interest. The authors proposed an easily calculated composite score for predicting the risk of advanced fibrosis in patients with non-alcoholic fatty liver disease (NAFLD), called the BARD score: the weighted sum of the three variables (body mass index (BMI) ≥28 = 1 point, aspartate aminotransferase/alanine aminotransferase ratio (AAR) ≥0.8 = 2 points, diabetes = 1 point). When a BARD score of 2–4 was used, the area under the receiver operating characteristic curve (AUROC) was found to be 0.81 with an odds ratio (OR) of 17 (95% CI 9.2 to 31.9) for detecting advanced fibrosis. The positive predictive value (PPV) and negative predictive value (NPV) were 43% and 96%, respectively. We studied the reliability of the BARD score for identifying the risk of advanced fibrosis in Japanese patients with NAFLD.

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REFERENCES


Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Simple steatosis and NASH fibrosis 0–2 (n = 76)</th>
<th>NASH fibrosis 3–4 (n = 46)</th>
<th>p Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 years</td>
<td>45 (59)</td>
<td>37 (80)</td>
<td>0.016</td>
<td>2.8 (1.2 to 6.7)</td>
</tr>
<tr>
<td>Female gender</td>
<td>42 (55)</td>
<td>33 (72)</td>
<td>0.070</td>
<td>2.1 (0.9 to 4.5)</td>
</tr>
<tr>
<td>Body mass index ≥28 kg/m²</td>
<td>24 (32)</td>
<td>15 (33)</td>
<td>0.906</td>
<td>1.0 (0.5 to 2.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (24)</td>
<td>18 (39)</td>
<td>0.070</td>
<td>2.1 (0.9 to 4.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (28)</td>
<td>24 (52)</td>
<td>0.007</td>
<td>2.9 (1.3 to 6.1)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>52 (68)</td>
<td>20 (43)</td>
<td>0.007</td>
<td>0.4 (0.2 to 0.8)</td>
</tr>
<tr>
<td>AST/ALT ≥0.8</td>
<td>16 (21)</td>
<td>27 (59)</td>
<td>&lt;0.0001</td>
<td>5.3 (2.4 to 11.9)</td>
</tr>
<tr>
<td>Platelets &lt;200 × 10⁹ cells/l</td>
<td>25 (33)</td>
<td>36 (78)</td>
<td>&lt;0.0001</td>
<td>7.3 (3.1 to 17.1)</td>
</tr>
<tr>
<td>Albumin &lt;4.1 g/dl</td>
<td>24 (32)</td>
<td>32 (70)</td>
<td>&lt;0.0001</td>
<td>5.0 (2.2 to 10.9)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NASH, non-alcoholic steatohepatitis.

Figure 1 Simple steatosis plus non-alcoholic steatohepatitis (NASH) with fibrosis stages 0–2 vs NASH with fibrosis stages 3–4. AUC, area under the curve.
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