MINI REVIEW

The role of hypercoagulability in liver fibrogenesis

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Summary  The development of hepatic fibrosis on a background of chronic liver injury represents a complex disease trait modulated through the interaction of host genetic factors and environmental influences. Early observations that hepatic inflammation and cirrhosis are associated with the presence of microthrombi within the hepatic vasculature and fibrin/fibrinogen deposition were followed by epidemiological studies showing that carriage of the Factor V Leiden (FvL) mutation, protein C deficiency and increased expression of factor VIII are associated with accelerated progression to cirrhosis in a chronic hepatitis C infection. Additional data suggest that these factors may influence fibrogenesis in many forms of chronic liver disease and extra-hepatic fibrotic processes. Drawing evidence both from liver research and studies of fibrogenesis in other organ systems, two hypotheses may explain how activity of the coagulation cascade influences the rate of hepatic fibrogenesis: tissue ischaemia and parenchymal extinction and direct thrombin mediated stellate cell activation via PAR-1 cleavage. Drawing on preclinical and clinical studies we discuss the evidence for a role for coagulation cascade activity in hepatic fibrogenesis and explore the proposed pathogenic mechanisms that lead to stellate cell activation. The corollary of an association between hypercoagulation and increased fibrosis is that interference with the coagulation cascade may reduce hepatic fibrosis. We conclude this article by examining the implications for future therapeutic intervention.

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Introduction  The development of fibrosis following chronic injury, irrespective of aetiology, is best considered a complex disease trait that may be influenced by the interaction of host genetic factors, the pathogen and other coincidental environmental influences. Tissue damage initiates a “wound healing response” on a whole organ scale that continues until the causative factor is removed [1,2]. Hepatic fibrogenesis is mediated by the activation of the hepatic stellate cell (HSC) to a smooth muscle myofibroblast-like phenotype characterised by alpha-smooth muscle actin (\(\alpha\)-SMA) and desmin expression, type I/III collagen secretion and release of tissue inhibitor of metalloproteinase 1 (TIMP-1) that prevents matrix metalloproteinase mediated collagen remodelling [3]. When injury or infection persists, the

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normal wound-healing response continues, leading to accumulation of scar tissue and eventually cirrhosis. Removal of the underlying aetiology before the development of cirrhosis and liver failure is the primary therapeutic goal in treating chronic liver disease. However this is not always possible and so a secondary goal would be to inhibit progression of hepatic fibrogenesis. Currently there are no effective, well-tolerated antifibrotic drugs that are generally available. Thus, the mechanisms by which fibrosis and the progression to cirrhosis occur are an area of intense research interest.

Liver disease—a procoagulant state?

A complex balance between endogenous procoagulant and anticoagulant factors exists in patients with liver disease [4]. As disease progresses profound changes in the haemostatic system occur including decreased circulating levels of coagulation factors and inhibitors, reduced levels of fibrinolytic proteins as well as thrombocytopenia and altered platelet function [5]. A more full discussion of these changes and there consequences are outside the scope of this article however they have recently been reviewed [4, 5]. Whilst the clinical manifestations of liver disease are frequently related to bleeding, hypercoagulability due to decreased levels of protein C, protein S, antithrombin, α2-macroglobulin and heparin cofactor II as well as increased levels of factor VIII and von Willebrand factor (vWF) play an important and under-recognised role in many aspects of acute and chronic liver disease [4, 5]. Indeed, there is growing recognition that normal thrombin generation may proceed in advanced cirrhosis despite apparent derangement of conventional coagulation tests such as prothrombin time [6]. To date, only a fraction of the factors that account for the observed variability in fibrotic disease progression are known [7, 8]; the available evidence would suggest that coagulation status is amongst them.

A role for clotting in hepatic fibrogenesis

The presence of microthrombi is associated with hepatic damage

Large thrombi occluding the hepatic vein are generally accepted as a cause of hepatic fibrosis in Budd-Chiari syndrome [9]. The presence of intrahepatic microvascular thrombi associated with fibrosis in humans was initially described in the cirrhotic liver post-mortem [10, 11]. Wanless et al. observed that the extent and distribution of microthrombi within branches of the hepatic vein and portal vein correlated with progression of hepatic fibrosis in a number of pathologies including HCV, HBV, PBC, alcoholic liver disease and cardiac cirrhosis [10, 11]. However, these observations are predated by almost a decade by animal studies examining the effects of acute murine hepatitis virus (MHV3) infection in two inbred strains of mice, C3HeB/FeJ and Balb/cJ. Examination of corrosion casts taken of the hepatic microvasculature demonstrated accumulation of microthrombi in areas of tissue necrosis proportional to disease severity and provides some of the earliest evidence for the role of coagulation cascade activation as a driver of liver injury [12–14]. This effect, which may be mediated via increased expression of the prothrombinase Fg2/Fibroleukin on the surface of hepatic endothelial cells, is induced by viral infections including hepatitis B [15]. Further support for the role of coagulation in hepatic fibrosis comes from rodent studies using both acute administration or sustained exposure to carbon tetrachloride (an agent used to induce oxidative stress mediated liver injury in vivo to model liver fibrosis) which also stimulates fibrin and fibrinogen deposition of within the hepatic microcirculation [16].

Procoagulant states are associated with more advanced hepatic fibrosis

Recognition that known factors could only account for a fraction of the interpatient variation in observed disease progression and fibrosis in chronic liver disease has led to the search for genetic disease modifiers that may also influence pathogenesis. Almost a further decade after Wanless’ original description of microthrombi in human cirrhosis, Papateodoridis et al. demonstrated that chronic viral hepatitis patients with advanced fibrosis (Ishak stage 4–6) were significantly more likely to have thrombophilia related to a deficiency of protein C, antithrombin III and plasminogen than those with more mild disease (Table 1) [17]. Shortly afterwards a candidate gene association study conducted by a European consortium reported that heterozygote carriage of the Factor V Leiden (FvL) mutation was associated with a 3.28-fold increased risk of rapid fibrosis progression in a Caucasian hepatitis C cohort [8]. This has since been independently validated in a second cohort [18]. However a third study in women infected by HCV-contaminated anti-D immunoglobulin could not replicate these findings [19]. This apparent inconsistency may be due to the extremely low overall fibrosis stage observed in the all female study cohort, whilst the effect of FvL carriage in the original article was most pronounced in males [8, 19]. Other reports have linked protein C deficiency, increased expression of factor VIII and hyperhomocysteinaemia to advanced HCV fibrosis [20]. Translational studies using murine models of liver fibrosis have shown that C57BL/6 mice carrying the prothrombotic Factor V Leiden (FvL) mutation exhibit more severe hepatic fibrosis after chronic carbon tetrachloride exposure than wildtype littermates [21]. This effect has also been described in the bleomycin inhalation mouse model of pulmonary fibrosis where FvL carriage is again associated with more severe disease [22].

Turning this paradigm around, further support for the role of coagulation in hepatic fibrogenesis comes from studies examining the natural history of liver disease in a cohort of 185 HCV infected (HIV negative) haemophiliac patients. These suggest a slow progression of liver fibrosis with only 3% (95 CI 0.4–6%) having liver related deaths in one study. Of those six patients that did develop liver related morbidity, five were known to also take excess alcohol and one died due to a complication from a liver biopsy [23]. Thus it would seem that whilst a hypercoagulant, prothrombotic, state promotes accelerated fibrogenesis, an antithrombotic state is associated with slower fibrosis.
Table 1  Studies showing an association between thrombophilia and advanced liver fibrosis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cohort n (Male%)</th>
<th>Factors</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papatheodoridis, 2003</td>
<td>HBV &amp; HCV n = 90 (71%)</td>
<td>Protein C Deficiency</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antithrombin III Deficiency</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasminogen Deficiency</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activated Protein C Resistance</td>
<td>0.075</td>
</tr>
<tr>
<td>Wright, 2003</td>
<td>HCV n = 352 (56%)</td>
<td>Factor V Leiden (APC Resistance)</td>
<td>0.004 (OR 3.28)</td>
</tr>
<tr>
<td>Poujol-Robert, 2004</td>
<td>HCV n = 559 (NA)</td>
<td>Factor V Leiden (APC Resistance)</td>
<td>0.003 (OR 4.0)</td>
</tr>
<tr>
<td>Poujol-Robert, 2004</td>
<td>HCV n = 68 (63%)</td>
<td>Protein C Deficiency</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated Factor VIII Level</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperhomocystinaemia</td>
<td>0.023</td>
</tr>
<tr>
<td>Goulding, 2007</td>
<td>HCV n = 210 (0%)</td>
<td>Factor V Leiden (APC Resistance)</td>
<td>NS</td>
</tr>
<tr>
<td>Martinelli, 2008</td>
<td>HCV n = 287 (56%)</td>
<td>PAR-1 Polymorphism (C-1426T)</td>
<td>0.04</td>
</tr>
<tr>
<td>Papatheodoridis, 2009</td>
<td>NAFLD/NASH n = 60 (52%)</td>
<td>Increased fibrosis in patients with at least one prothrombotic risk factor</td>
<td>0.002</td>
</tr>
</tbody>
</table>

APC: Activated Protein C.

Table 2  Trials examining anticoagulation as antifibrotic therapy.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Organ/disease studied</th>
<th>Model</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Liver</td>
<td>Mouse: CCl4</td>
<td>Reduced fibrosis</td>
<td>[21]</td>
</tr>
<tr>
<td>LMWH</td>
<td>Liver</td>
<td>Rat: CCl4</td>
<td>Reduced fibrosis</td>
<td>[47,48]</td>
</tr>
<tr>
<td>LMWH</td>
<td>Liver</td>
<td>Rat: Bile Duct Ligation</td>
<td>Reduced fibrosis</td>
<td>[47,48]</td>
</tr>
<tr>
<td>Thrombin inhibitor (SSR182289)</td>
<td>Liver</td>
<td>Rabbit: Cholesterol diet &amp; Diethylstilbestrol</td>
<td>Reduced fibrosis</td>
<td>[49]</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Liver</td>
<td>Mouse: Bleomycin inhalation</td>
<td>Reduced fibrosis</td>
<td>[26]</td>
</tr>
<tr>
<td>Heparin / Urokinase</td>
<td>Lung</td>
<td>Mouse: Bleomycin inhalation</td>
<td>Reduced fibrosis</td>
<td>[50]</td>
</tr>
<tr>
<td>Factor Xa inhibitor (ZK 807834)</td>
<td>Lung</td>
<td>Mouse: Bleomycin inhalation</td>
<td>Reduced fibrosis</td>
<td>[45]</td>
</tr>
<tr>
<td>Dagabatran</td>
<td>Lung</td>
<td>Mouse: Bleomycin inhalation</td>
<td>Anti-inflammatory and antifibrotic effects</td>
<td>[54]</td>
</tr>
<tr>
<td>Factor Xa inhibitor (Rivaroxaban)</td>
<td>Liver</td>
<td>Mouse: Thioacetamide Human (Trial)</td>
<td>Reduced fibrosis</td>
<td>[51]</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Idiopathic Pulmonary Fibrosis</td>
<td>Human (Trial)</td>
<td>Reduced mortality</td>
<td>[53]</td>
</tr>
<tr>
<td>LMWH</td>
<td>Chronic viral hepatitis related liver fibrosis</td>
<td>Human (Trial)</td>
<td>Reduced fibrosis</td>
<td>[52]</td>
</tr>
</tbody>
</table>

Pathogenic mechanisms

Drawing evidence both from liver research and studies of fibrogenesis in other organ systems, the current literature provides two mechanisms that could explain how activity of the coagulation cascade may effect changes in the rate of hepatic fibrosis progression. Both are biologically plausible and support a role for the coagulation system in the control of tissue repair and remodelling.

Parenchymal extinction: intrahepatic microthrombi causing tissue ischemia and fibrosis

Based on their observation that the extent and distribution of microthrombi within branches of the hepatic vein and portal vein correlated with progression of hepatic fibrosis, Wanless et al. proposed that micro-infarcts were the critical event in the genesis of fibrous septa and hence cirrhosis [10,11]. They postulated that occlusive thrombi, initiated by intimal injury due to adjacent hepatic necroinflammation, form within branches of the hepatic vein and portal vein and disrupt the flow of blood (Fig. 1). Obliteration of small hepatic and portal venules causes congestion and reactive hyperaemia. Together with VEGF induced angiogenesis, this leads to an imbalance between sinusoidal inflow and outflow leading to congestion, exudation and haemorrhage [10,11]. The consequent sinusoidal injury and tissue ischaemia causes hepatocyte apoptosis and collapse of the region between the central veins and their adjacent portal tracts [10,11]. The resulting parenchymal extinction lesion (PEL) may be defined as the irreversible loss of contiguous hepatocytes from a region, and replacement by fibrous tissue. Cirrhosis occurs when small areas of parenchymal
Hypercoagulability in Liver Fibrosis

Cells from both humans and rodents have been shown to express PAR-1, rodents also expressed PAR-4 although this was not tested in the human studies [34, 35]. Acting via PAR-1, thrombin is chemotactic for monocytes and mitogenic for smooth muscle cells, fibroblasts and hepatic stellate cells. Further, activation of PAR-1 has been shown to facilitate the αvβ6 integrin-dependent post-translational activation of latent TGFβ1, a key mediator of fibrogenesis [36].

In vitro studies using selective PAR-1 and PAR-4 agonists demonstrate that these are able to induce stellate cell activation [34]. Activation of PAR-1 by thrombin mediated proteolytic cleavage leads to rapid stellate cell activation and secretion of extracellular matrix proteins, tissue remodelling and fibrogenesis (Fig. 2) [34, 35, 37]. Several studies have established that hepatic PAR-1 expression is increased by liver injury, sensitising stellate cells to thrombin-mediated activation. These include both acute and chronic hepatitis [35] and cholestatic liver injury caused by bile duct ligation [34]. Tissue factor and PAR-1 expression have also been shown to be increased in patients with cholestatic liver diseases including primary biliary cirrhosis and sclerosing cholangitis and in a murine experimental model of cholestasis induced by α-naphthylisothiocyanate [38]. These observations suggest that substrate (PAR-1) availability ceases to be a rate limiting factor at sites of inflammation. Thus, a prothrombotic state, characterised by an increase in the basal levels of thrombin generation within the circulation, may contribute to fibrogenesis by enhancing direct activation of stellate cells. In this way, increased thrombin production, due to failure of the Thrombin/Thrombomodulin negative feedback loop via Activated Protein C (APC), as occurs in carriage of the FvL mutation, could amplify PAR-1 signalling (Fig. 2). This model for the role of thrombin and FV in the genesis of hepatic fibrosis is supported by studies that demonstrate fibrosis is ameliorated by administration of a PAR-1 antagonist [34]. Hepatic fibrosis related to α-naphthylisothiocyanate induced cholestatic liver disease is ameliorated in both tissue-factor and PAR-1 knockout mice where the observed up-regulation of αvβ6 integrin expression on intrahepatic bile duct epithelial cells is blunted, reducing TGFβ1 acti-

![Figure 1](image_url)

**Figure 1** Natural history of parenchymal extinction & fibrous septa formation. A Normal liver with patent portal and hepatic veins. B Inflammatory injury causes venous thrombosis (black). The consequent hepatocyte ischaemia and death leads to parenchymal extinction. C Extinction allows tissue to collapse so that adjacent portal tracts and hepatic veins are approximated. D Regions of extinction are replaced by fibrous septa. The obliterated venules are no longer evident. Reproduced from Anstee et al. with permission [28].
PAR-1 mediated actions of thrombin in stellate cell activation. Inflammation within the hepatic parenchyma increases expression of Tissue Factor, a key initiator of the coagulation cascade, and the thrombin receptor, PAR-1. Inflammation thus primes both the generation of thrombin and its downstream signalling activity. In the presence of the FvL mutation, the normal Thrombin/Thrombomodulin negative feedback loop via Activated Protein C (APC) that limits thrombin production is ineffective. This allows thrombin generation to proceed unchecked in a hepatic environment that is already sensitised for PAR-1 mediated stellate cell activation both directly and via platelet released PDGF. (TM, thrombomodulin).

Reproduced from Anstee et al. with permission [28].

evation [38]. Similarly, PAR-1 knockout mice are protected from bleomycin inhalation induced pulmonary fibrosis [39]. Platelets in humans express PAR-1 and PAR-4 (mice express PAR-3 and PAR-4) [40]. Thus, in addition to direct PAR mediated stellate cell activation, platelet degranulation and the release of platelet derived growth factor (PDGF), another potent stellate cell activator, may be triggered via the PAR receptor (Fig. 2) [41].

The role of factor-Xa/PAR-2 signalling in hepatic fibrosis is less well characterised however there has been a recent increase in interest in its role across a range of progressive fibrotic diseases. PAR-2 expression is highly expressed during acute and chronic inflammation in lung tissue [42], pancreatic fibrosis [43] and renal interstitial fibrosis where PAR-2 expression and αSMA expression were correlated [44]. In vitro studies have also shown that factor Xa triggers a pro-inflammatory and profibrotic response in fibroblasts via PAR-2 activation including cellular proliferation, migration and myofibroblast differentiation characterised by αSMA production, MCP-1 and IL-6 secretion and TGFβ expression [31]. The relative contribution of PAR-1 versus PAR-2 signalling remains unclear with some studies demonstrating that factor Xa signalling via PAR-1 remains the more important although this may alter in different tissues [45].

Taken together, these data place thrombin/factor Xa mediated PAR signalling as effectors of direct stellate cell activation, indirect stellate cell activation via PDGF release and post-translational TGFβ activation — all driving fibrogenesis. The relevance of this mechanism is further supported by a gene-association study in two separate cohorts of HCV patients that showed rapid hepatic fibrosis associated with carriage of a C-1426T transition mutation in the 5' regulatory region of the PAR-1 gene [46].

The parenchymal extinction hypothesis and the PAR-1/2 mediated stellate cell activation hypothesis are not mutually exclusive, nor are they the only mechanisms through which stellate cell activation is mediated [3,29]. Venulitis resulting from adjacent parenchymal inflammation may result in thrombosis more readily in the presence of a thrombophilic condition. However, whilst data from several sources supports coagulation cascade activation as a
driver of fibrosis, experimental data supporting parenchymal extinction remains sparse.

**Potential therapeutic implications**

A corollary of the association between hypercoagulation and increased fibrosis is that interference with coagulation cascade activation, thrombin generation or its downstream activity may reduce hepatic fibrosis. Several studies support this hypothesis (Table 2).

**Therapeutic studies in animal models**

As described above, administration of a PAR-1 antagonist reduces hepatic fibrosis and stellate cell activation in the rat bile duct ligation model [34]. It has been demonstrated that carbon tetrachloride induced hepatic fibrosis in C57BL/6 mice may be slowed by concomitant administration of coumarin (warfarin) [21]. Similar results have also been reported in this and other models of liver damage using low molecular weight heparin [47,48], the synthetic thrombin inhibitor SSR182289 [49], and Ximelagatran (Anstee et al., unpublished data). Studies in the rabbit model of fibrosing steatohepatitis induced by a combination of diethylstilbestrol injections and a high cholesterol diet have reported that concomitant administration of dipyridamole (a pyrimidopyridine derivative with antiplatelet and vasodilator properties) reduced hepatic fibrosis [26]. Aerosolized heparin and urokinase are similarly effective in ameliorating bleomycin induced pulmonary fibrosis [50]. A recent paper has also demonstrated that increased pulmonary expression of factor X contributes to the post-bleomycin inhalation fibrotic response through PAR-1 signalling and that this effect may be ameliorated using a direct factor Xa inhibitor [45]. Similarly, a study presented in abstract form shows that factor Xa inhibition with Rivaroxaban is an effective antifibrotic in the murine thiocetamide induced liver fibrosis model [51].

**Therapeutic efficacy in clinical practice**

Although existing data does not support the routine use of therapeutic anticoagulation as an antifibrotic therapy outside clinical trials, it is becoming evident that modulating the activity of the coagulation cascade may be a clinically relevant therapeutic target for development of novel antifibrotic agents. One small study has been published suggesting efficacy of low-molecular weight heparin as an antifibrotic in patients with chronic HBV [52] however long term heparin use is associated with several undesirable complications and so alternative agents should be trialled. Pursuing an analogous hypothesis, a Japanese group has also reported reduced mortality from a pilot study of coumarin (warfarin) treatment in patients with idiopathic pulmonary fibrosis [53]. The choice of agent and clinical efficacy will need to be fully evaluated. Suitable agents may include coumarin, direct thrombin inhibitors or antiplatelet drugs such as dipyridamole. Despite the withdrawal of the thrombin inhibitor Ximelagatran following reports of drug induced liver injury, several other agents are available for testing in this setting (e.g. Dabigatran etexilate is already licensed for prevention of venous thromboembolism in many countries and has been shown to reduce pulmonary fibrosis in mouse models [54,55]). In addition, the development of specific factor Xa inhibitors provides the opportunity to intervene earlier in the coagulation cascade: a potentially attractive option allowing reduced thrombin activation and also controlling direct factor Xa mediated signalling through PAR-1/PAR-2 cleavage, pilot data in animal models would support this approach across a number of organ systems [45,51].

As well as drug selection, the potential study population (and ultimately target patient groups) also require careful consideration. The concept of anticoagulation in the face of chronic liver disease is somewhat counter-intuitive given the risk of haemorrhage once portal hypertension is established. Antithrombotic/antifibrotic therapy may therefore be best reserved for the pre-cirrhotic patient. The majority of human studies in the setting of chronic progressive liver disease have been conducted in patients with HCV infection where there is an expanding cohort of patients with a progressive fibrotic liver that have not responded to current interferon-based antiviral therapy and who may benefit from alternative strategies targeted at delaying disease progression. Preliminary data in a small cohort of HCV infected non-responder patients indicates that an 8-week period of coumarin anticoagulation was well tolerated and associated with a reduction in liver stiffness as measured by transient elastography however no significant change in serum markers of fibrosis was observed in this short study [56]. The generally slow rate of progression of liver disease make trials in this setting challenging however post liver transplant patients infected with HCV are known to exhibit accelerated fibrosis and already undergo routine annual protocol biopsies in many centres. A multicentre trial (WAFT-C) examining the efficacy of coumarin based anticoagulation as an antifibrotic in the post-transplant chronic HCV population is currently recruiting at a number of UK centres.

**Conclusion**

The development of hepatic fibrosis on a background of chronic liver injury represents a complex disease trait modulated through the interaction of host genetic factors, the pathogen and other coincidental environmental influences. Early observations of hepatic inflammation and established cirrhosis associated with the presence of microthrombii within the hepatic vasculature and fibrin/fibrinogen deposition led to epidemiological studies examining prothrombotic risk factors and rate of hepatic fibrosis. Prothrombotic states have been associated with rapid progression to cirrhosis in a chronic HCV and NAFLD. Based on current literature, two complimentary hypotheses may be proposed that explain how activity of the coagulation cascade may influence the rate of hepatic fibrogenesis: tissue ischemia and parenchymal extinction and direct thrombin mediated stellate cell activation via PAR-1 cleavage. Current clinical data and in vivo models support a role for coagulation cascade activity in hepatic fibrosis mediated by activated factor X and the downstream events of thrombin activation. The corollary of an association between hypercoagulation and increased fibrosis is that interference with coagulation cascade may
reduce hepatic fibrosis. This is an intriguing and potentially novel therapeutic avenue towards amelioration of hepatic fibrosis in chronic disease states which may offer benefits for the growing cohort of patients in whom aetiology targeted therapies have proved unsuccessful. However, before such interventions may be considered in routine practice safety and efficacy will require validation in clinical trials.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


