Endothelial biomarker soluble CD146 suggests that angiogenesis plays an important role in progression of fibrosis in liver disease

Efrossini Nomikou¹, Alexandra Alexopoulou², Larisa Vasilieva², Spyridon P. Dourakis²

¹First Regional Transfusion and Haemophilia Centre, Hippokration General Hospital, Athens, Greece
²2nd Department of Medicine, Medical School, University of Athens, Hippokration General Hospital, Athens, Greece

Correspondence: Alexandra Alexopoulou
E-mail: alexopou@ath.forthnet.gr
Received: July 22, 2015
Published online: September 02, 2015

CD146, an element of the endothelial junction- has been evaluated in several pathological conditions with altered endothelial function but never before in patients with liver disease. As angiogenesis and inflammation were implicated in the development of liver fibrosis, we have explored this suggestion by evaluating levels of sCD146 in a group of patients with chronic liver diseases (CLD) and in cirrhotic patients. The results indicated that there is a clear connection between sCD146 levels and the progression of liver disease. They can differentiate noncirrhotic patients with CLD from cirrhotics, supporting the usefulness of CD146 in the noninvasive diagnosis of liver cirrhosis. Furthermore, our findings provided evidence of sCD146 upregulation in decompensated compared to compensated cirrhosis and sCD146 values were clearly associated with Model for End Stage Liver Disease (MELD) score. Thus, by using an easy to perform ELISA method, we demonstrated that sCD146 can accurately distinguish advanced fibrosis and prognosticate decompensation in cirrhosis.

Keywords: sCD146; endothelial junction; angiogenesis; fibrosis; cirrhosis

To cite this article: Efrossini Nomikou, et al. Endothelial biomarker soluble CD146 suggests that angiogenesis plays an important role in progression of fibrosis in liver disease. Inflamm Cell Signal 2015; 2: e925. doi: 10.14800/ics.925.

Introduction

The cell adhesion CD146 (S-Endo 1 Ag), “a member of the immunoglobulin superfamily” also referred as MUC18, was lately reported as a new element located at the endothelial cell-to-cell junction [1]. Intracellular junctions regulate the contact between adjacent endothelial cells, maintain integrity and modulate several functions of the endothelium [2, 3].

CD146 is a transmembrane glycoprotein acting as a signaling molecule expressed “in all types of human endothelium, irrespective of the anatomic site of vessel calibers” [4]. It takes part in the regulation of cell cohesion [5, 6] as it was revealed by its regulated expression during monolayer formation, facilitates cell-cell interactions and reflects endothelial remodeling. A soluble form of CD146 (sCD146) was recently identified in “the supernatant of cultured human endothelial cells and in normal human plasma” [7]. The presence of the soluble form in normal individuals may reflect the physiological turnover of junctional adhesive protein [8].

Soluble CD146 levels have been also evaluated in pathological conditions with altered endothelial function. Particularly, the levels of sCD146 were assessed in chronic renal insufficiency, in hemodialysis patients with atherosclerosis and in those with inflammatory bowel disease [9-11]. In these studies, alterations of basal levels were attributed to modifications of junctional functions such as...
permeability and vessel proliferation” [10-12]. Bardin et al. [8, 12] showed increased CD146 levels in chronic renal insufficiency and in patients with active inflammatory disease suggesting that this might reflect altered endothelial permeability. Kaspi et al. [12, 13] suggested that as sCD146 composes a novel factor with angiogenic features, it could be implicated in the management of the vascular development of placenta by acting on extravillus trophoblast. Also, as it is linked to the inflammatory response by boosting transmigration of monocytes, Kaspi et al. showed that women with a history of obstetric complications had significantly higher sCD146 levels [12].

Saito et al [10] proposed that as endothelial dysfunction associated with inflammation is probably liable for accelerated atherosclerosis in chronic renal insufficiency, elevation in CD146 levels may be linked to the development of arteriosclerosis obliterans regardless of renal function. sCD146 probably is a more accurate marker than carotid intima-media thickness for detection of diabetic patients prone to develop atherosclerosis [14]. Since binding of CD146 affects the transition of monocytes through the endothelium, the monocyte-CD146 interaction probably stands for a future target to restrict atherosclerotic plaque progression.

Figarella-Branger et al [15] observed raised levels of adhesion molecules involved in endothelial cell junctions (sCD146, sPECAM-1) in idiopathic inflammatory myopathies. Belotti et al [16] showed that endothelial cells in essential thrombocytemia are activated, implying important contribution of angiogenesis in this disease and proposing a significant endothelial role in the hypercoagulation observed in those patients.

Recently, CD146 has been involved in cancer research. It has been shown that high sCD146 levels at baseline associated with unfavorable prognosis and probably helped to predict outcome in patient’s candidate for surgery for non small cell lung cancer [17]. Thomann et al. [18] published their research which demonstrated that CD146 is overexpressed on a fraction of human hepatocellular carcinoma (HCC). Furthermore, by using monoclonal antibody anti-CD146 provided promising principle for the use of endothelial markers for the imaging and more importantly, for the therapy of HCC by intratumoral drug delivery.

CD146 IN Liver Disease

Angiogenesis, a process leading to the formation of “new capillaries by endothelial sprouting from pre-existing vasculature” [19, 20] has been correlated to the progression of fibrosis in chronic liver disease [21-25]. Recent studies, assessing the biomarkers’ contribution in endothelium function, have suggested that endothelium and intrahepatic angiogenesis are substantial for the evolution of fibrosis [26-28].

Till now, there is “no well-recognized surrogate biomarker that can accurately detect the presence of histologically confirmed cirrhosis” [24, 25]. Since sCD146 can provide evidence for endothelial activation and proliferation, we investigated its performance in estimating liver fibrosis and cirrhosis, its relationship with Model-for-End-Stage-Liver Disease (MELD) score and its utility in differentiating compensated from decompensated cirrhosis [29].

We found that median sCD146 values were considerably higher in patients with cirrhosis in comparison with those with non-cirrhotic chronic liver disease (CLD) or to healthy controls. Moreover, patients with compensated cirrhosis had “higher levels than non-cirrhotic CLD patients but lower than patients with decompensated cirrhosis”. ROC curve analysis showed that sCD146 levels accurately differentiated patients with cirrhosis from non-cirrhotics with CLD. In addition, sCD146 offered good diagnostic accuracy for differentiating compensated from decompensated cirrhosis. Furthermore, levels of sCD146 in cirrhotics were highly correlated with MELD score, Internal Normalized Ratio and bilirubin and negatively with albumin, providing evidence of a sCD146 up-regulation in decompensated compared to compensated cirrhosis.

We also found that sCD146 levels were correlated with inflammatory markers of liver disease such as aminotranferases. Chronic and persistent inflammation correlates with liver disease progression. Chemokine interactions stimulate the regional release of factors promoting angiogenesis by hepatic stellate and sinusoidal endothelial cells, key cells type in fibrosing liver injury [30]. CD146 is involved in inflammatory response by boosting monocyte transition, exhibiting chemotactic function on endothelial cells [31, 32]. These combined properties of CD146-involved in angiogenesis and inflammation could support our results illustrating that sCD146 levels were significantly correlated with both activity and severity of liver disease. This biomarker might therefore be a supplementary tool for clinicians in assessing progression of liver disease.

Our results are in accordance with previous studies that showed high levels of CEC (circulating endothelial cells) and EPC (endothelial progenitor cells) in cirrhotic patients [33-35] emphasizing the role of liver angiogenesis during progression of disease. Bone marrow derived circulating EPCs take part to neovascularisation in normal and pathological conditions and CECs are increased in patients with vascular injury and
endothelial dysfunction [36]. Endothelial damage and angiogenesis have been linked to the evolution of fibrosis in chronic liver diseases, since angiogenic cytokines expressed by activated stellate cells induce configuration of new vessels by resident endothelial cells and generation of collagen [37].

Biomarkers different from CD146 and non-related to angiogenesis were used as fibrosis-related parameters. Recently, Zhang Da-Wei et al. [38] suggested that HAb18G/CD147 – “an extracellular matrix metalloproteinase inducer - also a member of the immunoglobulin superfamily”, promotes fibrosis in cirrhotic liver. They demonstrated that HAb18G/CD147 expression was associated with the Child–Pugh grade, denoting an increased level of HAb18G / CD147 in the end stage of chronic liver disease, a finding similar to our observations. In addition, soluble CD163, an indicator of macrophage activation was recently found to be elevated in advanced cirrhosis and hepatic venous pressure gradient [39]. CD163 fibrosis score was also found to be superior to APRI and FIB-4 for the diagnosis of advanced fibrosis in hepatitis C virus infection [40].

To summarize our findings, we demonstrated that sCD146 levels are helpful in differentiating non-cirrhotic patients with CLD from cirrhotics. In particular, sCD146 values were considerable higher in patients with cirrhosis in comparison with non-cirrhotics with CLD. The clear cut-offs of the sCD146 in differentiating cirrhotics from CLD support the usefulness of CD146 in the non-invasive diagnosis of liver cirrhosis. The sCD146 values were found to be well correlated with MELD score which is a reliable prognostic marker for intermediate term mortality in cirrhosis [41]. Therefore, it could also be used as a surrogate marker to improve the predictive value of current clinical scores in patients with cirrhosis.

In conclusion, we demonstrated that sCD146 is emerging as an accurate, non-invasive biomarker, which can credibly distinguish advanced fibrosis and prognosticate decompensation of cirrhosis. Antibodies against CD146 molecules may as well be used as potential “target for anti-fibrotic therapy” but further investigation is needed for conclusions to be drawn.

Conflicts of interest

The authors have declared that no competing interests exist.

Abbreviations

CEC: circulating endothelial cells; CLD: chronic liver diseases; EPC: endothelial progenitor cells; HCC: hepatocellular carcinoma.

Author contributions

Efrossini Nomikou, Alexandra Alexopoulou, Larisa Vasilieva participated in drafting the paper, analysis and interpretation of the data. Spyridon Dourakis participated in design and revising the article.

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