Significance of Soluble Urokinase Plasminogen Activator Receptor in Liver Cirrhosis

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Amer Mohamed Hegazy

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List of Abbreviations

AIDS	Acquired immune deficiency syndrome
ALD	alcoholic liver disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ASMA	anti–smooth muscle antibody
AST	aspartate aminotransferase
ATF	Amino-terminal fragment of the A-chain in uPA
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CPT	Child-Pugh Turcotte
ECM	Extracellular matrix
EGF	Epidermal growth factor
ELISA	Enzyme linked immunosorbent assay
EVL	endoscopic variceal ligation
EVO	endoscopic variceal obturation
FGF	Fibroblast growth factor
FPRL	Formyl peptide receptor-like
GGT	gamma glutamyl transpeptidase
GOV	gastroesophageal varices
GPI	Glycosyl-phosphatidyl-inositol
HA	hyaluronic acid
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HCC	Hepatocellular Carcinoma
HCV	hepatitis C virus
HE	hepatic encephalopathy
HIV	Human immunodeficiency virus
HSC	hepatic stellate cell
IFN	Interferon

IGV	isolated gastric varices
INR	international normalized ratio
LC	liver cirrhosis
LOLA	L-ornithine-L-aspartate
LPS	Lipopolysaccharide or endotoxin, a component of the gram negative cell membrane
LRP	Low-density lipoprotein receptor-related protein
MCP	Monocyte chemotactic protein
MELD	Model for End-Stage Liver Disease
MHE	minimal hepatic encephalopathy
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
PAI	Plasminogen activator inhibitor
PA-system	Plasminogen activation system
PBC	primary biliary cirrhosis
PCR	polymerase chain reaction
PMN	polymorphonuclear leukocyte
pro-uPA	Proenzyme of uPA (single-chain (sc)-uPA)
PSC	primary sclerosing cholangitis
PT	Prothrombin time
PTT	Partial thromboplastin time
(s)uPAR	Refers to both cell-bound uPAR and suPAR
SBP	spontaneous bacterial peritonitis
serpin	Serine protease inhibitor
suPAR	Soluble urokinase-type plasminogen activator receptor
suPAR(I)	Soluble/free one-domain suPAR
suPAR(I-III)	Soluble/shed three-domain suPAR
suPAR(II-III)	Soluble/shed two-domain suPAR
TGF	Transforming growth factor
TIPS	transjugular intrahepatic portosystemic shunt

TNF	Tumour necrosis factor
tPA	Tissue-type plasminogen activator
uPA	Urokinase-type plasminogen activator (two-chain (tc)-uPA)
uPAR	Urokinase-type plasminogen activator receptor (CD87)
uPAR(I)	Domain I of uPAR
uPAR(II)	Domain II of uPAR
uPAR(III)	Domain III of uPAR
uPAR(I-III)	Cell-bound three-domain uPAR
uPAR(II-III)	Cell-bound two-domain uPAR

Introduction and Aim of the Work

Liver fibrosis and its end-stage sequelae cirrhosis represent a major worldwide health problem **(Bedossa et al., 2003).** Cirrhosis is the most advanced stage of most types of chronic liver disease. It is defined as a diffuse disorganization of normal hepatic structure by extensive fibrosis associated with regenerative nodules. Hepatic fibrosis is potentially reversible if the causative agent is removed. However, advanced cirrhosis leads to major alterations in the hepatic vascular bed and is usually irreversible **(Desmet and Roskams, 2004).**

Inflammation has been identified as the major mechanism that promotes progression of chronic liver diseases, leading to hepatic fibrosis and cirrhosis (**Karlmark et al., 2008).**

At present, liver biopsy is the gold standard to assess the degree of intrahepatic inflammation. In clinical routine, non-invasive, longitudinally measurable biomarkers for local and systemic inflammation would be highly desirable, as they may allow early identification of patients at risk for cirrhosis or at risk for fatal outcome. Nevertheless, currently available laboratory parameters have limitations, because they either reflect hepatic biosynthetic capacity (e.g. albumin, pseudocholinesterase, international

normalized ratio or INR), hepatic cell death [e.g. alanine aminotransferase activity (ALT)], cholestatic damage [e.g. bilirubin, c-glutamyl transpeptidase (GT)] or inflammatory activation restricted to distinct leucocyte subsets [e.g. interleukin (IL)-8 for neutrophils, CXCL10 for T-lymphocytes, monocyte chemoattractant protein (MCP)-1 for monocytes] **(Castera, 2011).**

The urokinase plasminogen activator receptor (uPAR) is expressed on most leucocytes including neutrophils, lymphocytes, monocytes and macrophages, which are crucially involved in the pathogenesis of hepatic inflammation and fibrosis **(Blasi and Carmeliet, 2002 and Smith and Marshall, 2010).** Initially, the receptor has been described to localize the activation of plasminogen to the cell surface after binding of uPA, thus, providing a localized cell surface proteolytic activity **(Behrendt, 2004).** In addition to its functions in the proteolytic cascade, uPAR is a potent regulator of cell adhesion, migration, chemotaxis, proliferation and differentiation through intracellular signaling **(Blasi and Carmeliet, 2002).** In uPAR deficient mice, leucocyte migration is decreased towards sites of inflammation **(May et al., 1998).** Interestingly, uPA- as well as uPAR-knock-out mice were

protected from hepatic fibrosis in experimental liver injury models, possibly because of immunomodulatory effects of uPA in hepatic fibrogenesis **(Higazi et al., 2008).**

In addition to the membrane anchored form, uPAR can be found as a soluble molecule in the serum termed "Soluble urokinase plasminogen activator receptor" (suPAR) **(Blasi and Carmeliet, 2002).**

Functionally, full-length suPAR has been suggested to be a regulator of the uPAR/uPA interaction **(Thunø et al., 2009).** By competing with cell-bound uPAR, suPAR may function as a scavenger for uPA by inhibiting cell-associated plasminogen activation **(Mizukami and Todd, 1998 and Kruger et al., 2000)**.

Aim of the work

The aim of this study is to assess the significance of soluble urokinase plasminogen activator receptor (suPAR) in different grades of liver cirrhosis.

Chapter I: Liver Cirrhosis

Definition

The word cirrhosis comes from the Greek word kirrhos, which means orange yellow. Laennec gave cirrhosis its name kirrhos in 1819 in a brief footnote to his treatise De l'auscultation mediate **(Duffin, 1987)**.

Cirrhosis is the most advanced stage of most types of chronic liver disease. Cirrhosis is defined as a diffuse disorganization of normal hepatic structure by extensive fibrosis associated with regenerative nodules. Hepatic fibrosis is potentially reversible if the causative agent is removed. However, advanced cirrhosis leads to major alterations in the hepatic vascular bed and is usually irreversible **(Desmet and Roskams, 2004).** Cirrhosis is a progressive and severe clinical condition associated with considerable morbidity and high mortality. It leads to a wide spectrum of characteristic clinical manifestations, mainly attributable to hepatic insufficiency and portal hypertension **(Afdhal, 2004).**

Cirrhosis can remain compensated for many years before the development of a decompensating event **(D'Amico et al., 2006).** In most persons, approximately 80 to 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically **(Heidelbaugh and Bruderly, 2006)**. Decompensated cirrhosis is marked by the development of any of the following complications: jaundice, variceal hemorrhage, ascites, or encephalopathy **(D'Amico et al., 2006).**