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Journal of Cell Signaling

Opinion

# Role of SPOCK1 in the Development of Liver Fibrosis

**Akihiko Ren***

*Department of Functional Genomics, Chiba University Graduate School of Medicine, Chiba, Japan*

## INTRODUCTION

A fibrotic wound-healing response can be induced by chronic liver illnesses of various aetiologies, which results in liver fibrosis. Extracellular Matrix (ECM) deposition and distribution abnormalities are the characteristics of liver fibrosis, which prevents the normal liver from regenerating normally and ultimately leads to cirrhosis, liver failure, or even Hepatocellular Cancer (HCC). According to the aetiology of HCC, about 40% of cases are brought on by Hepatitis B Virus (HBV), 40% by Hepatitis C Virus (HCV), 11% by chronic alcohol abuse, and about 10% by other causes. Non-alcoholic fatty liver disease is becoming more common, and all of these aetiologies may cause liver fibrosis and create a favourable environment for tumour development. Worldwide, cirrhosis of the liver is currently the 11$^{th}$ most common cause of death approximately 1.16 million deaths annually. There is currently no approved anti-fibrotic medication, despite increased treatment strategy development over the previous 20 years. Therefore, extensive study into the mechanism of hepatic fibrogenesis is urgently required.

The primary cause of liver fibrosis is the activation of Hepatic Stellate Cells (HSCs). The vitamin-A-storing HSCs that are quiescent transdifferentiate into myofibroblasts during this process, providing them enhanced ability for ECM synthesis, proliferation, contraction, and migration. Senescence, deactivation, and induction of apoptosis are the key pathways for the removal of HSCs and the resolution of liver fibrosis. HSC activity is controlled by a variety of pathways and mediators. According to recent studies, the "big five," which include macrophages, myofibroblasts, matrix, mechanics, and miscommunication, are responsible for fibrosis. The ECM, where HSCs are found, not only supports them structurally but also regulates their biological functions. Therefore, researching how ECM elements affect HSC activation and liver fibrosis may help develop new anti-fibrotic treatments.

Matricellular proteins play a key role in the development of the embryo, the inflammatory response, tissue remodelling, and the evolution of tumours. These non-structural proteins, which are found in the cytoplasm or secreted into the ECM, regulate the interaction between matrix and cells. Matricellular protein's function in liver fibrosis has received a lot of interest recently. For instance, osteopontin enhances HSC activation and collagen deposition and is expressed more frequently in several chronic liver fibrosis models. Sparc/osteonectin, cwcv and kazal like domain proteoglycan 1 (SPOCK1) is a matricellular protein that is a member of the Secreted Protein, Acidic, and Rich in Cysteine (SPARC) family. Testican-1, another name for SPOCK1, was first identified in the human testis, and extant studies has shown that SPOCK1 is expressed in a variety of organs. SPOCK1's role is not entirely understood, however it may be connected to protease inhibition. SPOCK1 primarily has oncogenic roles in a variety of cancers, including HCC, gallbladder cancer, gastric cancer, etc., by boosting proliferation, invasion, and survival. Although it is commonly accepted that liver fibrosis represents a precancerous stage of HCC, it is still unclear how SPOCK1 contributes to liver fibrogenesis.

## DESCRIPTION

In the recent study, it is clarified that SPOCK1's functions, processes, and implications in liver fibrosis for the first time. In both fibrotic liver tissues from humans and rats as well as in activated primary rat HSCs, we discovered that SPOCK1 expression was markedly elevated. Then, we discovered that Platelet Derived Growth Factor (PDGF)-BB and Transforming Growth Factor (TGF)-1 were responsible for inducing SPOCK1 expression in HSCs. It's interesting to note that SPOCK1 has been implicated as a TGF-1 target gene in breast and lung cancer cells. Mainly focused on the method by which PDGF-BB upregulated SPOCK1 expression because it had a strong effect on its expression. Our results demonstrate that the phosphatidylinositol 3-kinase/protein kinase B/forkhead box M1 (PI3K/Akt/FoxM1) signalling pathway was activated by PDGF-BB to enhance SPOCK1 expression. PDGF-BB is well known for promoting HSC activation, proliferation, and migration. SPOCK1, a PDGF-BB target gene, was involved in the pro-fibrotic reactions caused by PDGF-BB. SPOCK1 increased HSC activation, proliferation, and migration by activating the PI3K/Akt signalling pathway. A curious relationship between PI3K/Akt activation and SPOCK1 expression has been found; specifically, PDGF-BB upregulates SPOCK1 expression by activating the PI3K/Akt pathway, and SPOCK1 reciprocally

**Correspondence to:** Akihiko Ren, Department of Functional Genomics, Chiba University Graduate School of Medicine, Chiba, Japan; E-mail: ren@akihiko.ac.jp

**Received:** 24-Dec-2022, Manuscript No. JCS-22-21159; **Editor assigned:** 26-Dec-2022, PreQC No. JCS-22-21159 (PQ); **Reviewed:** 09-Jan-2023, QC No. JCS-22-21159; **Revised:** 23-Mar-2023, Manuscript No. JCS-22-21159 (R); **Published:** 29-Sep-2023, DOI: 10.35248/2576-1471.23.8.345

**Citation:** Ren A (2023) Role of SPOCK1 in the Development of Liver Fibrosis. J Cell Signal. 8:345.

promotes the PI3K/Akt pathway, increasing the pro-fibrotic responses.

## CONCLUSION

Liver fibrosis prevents the normal liver from regenerating normally and ultimately leads to cirrhosis, liver failure, or even hepatocellular cancer. Extracellular Matrix (ECM) deposition and distribution abnormalities are the characteristics of liver fibrosis. There is currently no approved anti-fibrotic medication, despite increased treatment strategy development. SPOCK1 was first identified in the human testis, and extant studies has shown that SPOCK1 is expressed in a variety of organs. Although it is commonly accepted that liver fibrosis represents a precancerous stage of HCC, it is still unclear how this gene contributes to liver fibrogenesis.