Bile Acids Enhance Cellular Motility of the Hepatic Myofibroblast-Like Cell through the Regulation of p38/JNK Signaling

Yining Zhang, Tadashi Ikegami, Akira Honda, Bernard Bouscarel, Yasushi Matsuzaki

Graduate School of Comprehensive Human Science, University of Tsukuba, Japan
Tokyo Medical University Kasumigaura Hospital, Japan
Ibaraki Prefectural Institute of Health Science, Japan
The George Washington University Medical Center, USA
Liver fibrosis represents the consequences of a sustained wound healing response to acute and chronic injury.

Hepatic stellate cells (HSC), and liver myofibroblastic cells play a central role in liver fibrogenesis as the primary source of excessive extracellular matrix (ECM).
Hepatic Fibrosis and Bile Acids

Pro-fibrogenic role of bile acids in intra- and extra-hepatic cholestasis has been discussed.

Recent reports revealed an enhancement of proliferation in hepatic stellate cells (HSC) by GCDCA, implicating the contribution of BA in the progress of hepatic fibrosis (Svegliati-Baroni et al. Gastroenterology, 2005).
Hepatic Stellate Cell

- Kupffer cell
- Fibrosis
- Stellate cell
HSC Contraction and Portal Hypertension

Three dimensional structures of two pig HSCs. ×1000


M. Pizani and F. Marra et al, University of Florence
The Motility of activated HSC

Endothelial Cell

HSC

Hepatocytes
The Motility of activated HSC

HSC activation

Liver Injury
Liver Injury

HSC activation

Liver Injury
The Motility of activated HSC

Migration

ECM components
Aim
To investigate the effect of bile acids on the motility of activated HSC.

Materials
Activated HSC cell line established from CCl$_4$-treated rat liver (CFSC-2G).
Effect of GCDCA on Cell Proliferation

Percentage of CTL

1% FCS
10% FCS

CTL  GCDCA  TGF  GCDCA+TGF

*
Effect of GCDCA on Cell Attachment

- Uncoated Type I Collagen
- CTL
- TGF
- GCDCA

Percentage of CTL

- Uncoated
- Type I Collagen

* indicates a significant difference.
Wound Healing Assay

CTL

GCDCA

0 h 12 h
Bile Acid and Cell Spreading

Percentage of CTL

- 30 min
- 60 min
- 120 min

GCDCA

CTL
Lamellipodia Formation

CTL

GCDCA

Cells with Lamellipodia (%)

CTL

GCDCA
Phosphorylation of p38

WB: phospho-p38

- 10 min
- 1 h
- 24 h

Graph showing percentage of CTL at different time points with treatments:
- CTL
- TGF-beta
- GCDCA
Phosphorylation of JNK

WB: phospho-JNK

10 m

1 h

24 h

ctl

tgf-beta

gcdca

Percentage of CTL

0 10 min 1h 24h

ctl
tgf-beta
gcdca
p38 and Cell Spreading

Percentage of CTL

30 min 60 min 120 min

- CTL
- GCDCA
- SB
- GCDCA+SB

* indicates significant difference.
JNK and Cell Spreading

Percentage of CTL

- CTL
- GCDCA
- SP
- GCDCA+SP

30 min | 60 min | 120 min
Summary

- 50 µM GCDCA enhanced the proliferation of rat myofibroblastic-like cell line, CFSC-2G, in the presence of FCS.

- In the absence of FCS, GCDCA promoted the (1) wound healing and (2) cell spreading of CFSC-2G cell.

- GCDCA stimulated the activation of p38 and JNK.

- The effect of GCDCA on wound healing and cell spreading was significantly suppressed by p38 specific inhibitor.
Conclusion

Besides the reported effect of BAs on HSC proliferation, BAs can facilitate cellular motility, an essential characteristic of the activated HSCs through the induction of p38 and JNK phosphorylation.