Addressing liver fibrosis by TRAIL targetied to hepatic stellate cells

Arabpour, Mohammad

Addressing liver fibrosis by TRAIL targeted to hepatic stellate cells

Mohammad Arabpour

Printing of this thesis was financially supported by
Graduate School of Medical Sciences, University Medical Center Groningen

Cover design: Mohammad Arabpour, Matin Mehraban
Layout: Mohammad Arabpour
Printed by: IPSKAMP Drukkers, Enschede, The Netherlands
Cover and bookmark pictures are adopted from chapter 1 and chapter 3 of this book:
Top figure: Internalized TRAIL in a LX2 hepatic stellate cell
Bottom figure: Schematic depiction of TRAIL signaling in the liver

ISBN: 978-90-367-8767-3 (print)
ISBN: 978-90-367-8766-6 (digital)

university of groningen

Addressing liver fibrosis by TRAIL targeted to hepatic stellate cells

Exploring innovative targeting and therapies in liver fibrosis

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Friday 13 May 2016 at 14.30 hours

by

Mohammad Arabpour

born on 8 December 1979
in Shiraz, Iran

Supervisors
Prof. H.J. Haisma
Prof. K. Poelstra

Assessment Committee
Prof. Rob Hoeben
Prof. G.M.M. Groothuis
Prof. A.J. Moshage

Paranymphs
Marziyeh Toluee
Mahdi Hamidi Shishavan

Contents

Addressing liver fibrosis by tumor necrosis factor -related apoptosis-inducing ligand (TRAIL) targeted to hepatic stellate cells

Progressive liver fibrosis is the result of liver injury and is characterized by the excessive accumulation of extracellular matrices. When the progression of chronic liver disease remains unabated, the end-stage disease called liver cirrhosis develops, resulting in a total loss of liver function. Cirrhotic liver is associated with high mortality. As yet, no alternative preventive actions other than removing the underlying mechanisms of chronic liver disease have been introduced for curing liver fibrosis.

Various underlying disease conditions can promote liver fibrosis, but activated hepatic stellate cells are known to play a central role in the progression of the disease. The changes in gene expression pattern in hepatic stellate cells (HSC) during the activation process enable targeting these genes or their corresponding products as one successful approach in order to modulate HSC function and to inhibit the fibrotic process. Viral- or non-viral- mediated gene delivery of curative genes such as matrix metalloproteinases or proteins that interfere with signaling pathways of pro-fibrotic cytokines, i.e. soluble PDGFR, have previously been shown to slow the fibrotic process. However, due to the complex and ubiquitous nature of fibrosis such an approach does not allow for a full recovery. The elimination of activated hepatic stellate cells is a crucial step in the process of a natural resolution

and reversion of liver fibrosis. Previously, it has been shown that genes associated with inducing dead signals, such as TRAIL receptors, are upregulated on activated HSCs. Earlier studies have shown that the increase in TRAIL receptors on the surface of HSCs during activation is associated with an increase in HSC susceptibility to the TRAIL apoptosis effect. However, the short half-life of TRAIL *in vivo* and the development of anti-apoptotic signaling mechanisms that cause TRAIL resistance in activated HSCs have proven to be a major hurdle in enabling the therapeutic application of TRAIL as an option in treating liver fibrosis. This thesis deals with application of targeting TRAIL genes and proteins as a novel technology having the potential to successfully treat liver fibrosis. In fact, this is the very first study to demonstrate the potential application of TRAIL fusion protein and receptor specific TRAIL variants in targeting with dual functional applications that can selectively eliminate activated HSC and its pro-fibrotic function in the fibrotic liver.