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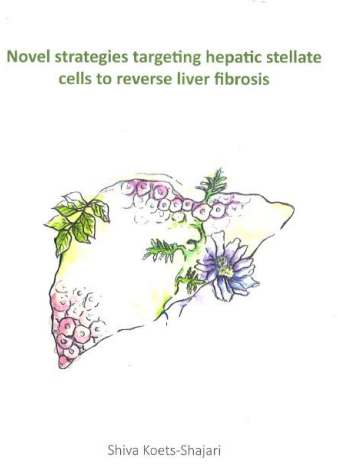

Samenvatting proefschrift
S.S. Koets-Shajari
'Novel Strategies targeting hepatic stellate cells to reverse liver fibrosis'

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Liver fibrosis is the formation of an abnormally large amount of scar tissue in response to a liver injury. It has the potential to progress into cirrhosis with a loss of mass, architecture and function leading to life-threatening complications. To date, there is no approved anti-fibrotic drug. Hepatic stellate cells (HSCs) play a key role in fibrogenesis in the liver. Any insult to the liver such as viral diseases or excessive alcohol consumption can trigger HSCs to transdifferentiate into myo-fibroblast-like cells, so-called activated HSCs, that produce abnormal amount of extracellular matrix proteins. Here, we explored the therapeutic effects of melatonin, esculetin and hydroxyurea on HSC activation. Additionally, we investigated the role of HSL in vitamin A homeostasis and activation of HSCs.
HSL is one of the key lipases in adipose tissue with a broad range of substrates including retinyl esters. However, its expression and function in liver are less known and the current data is limited to its cholesterol hydrolyzing activity in hepatocytes. We discovered that HSL is expressed in HSCs and functions as retinyl ester hydrolyzer. Numerous studies have examined the therapeutic properties of melatonin in a variety of liver injury models. We investigated the direct effect of melatonin on HSC activation. Our data revealed that melatonin suppresses HSC activation by down-regulating of 5-Lipoxugenase (5-LO), an enzyme involved in leukotrienes synthesis and generating inflammatory response. Esculetin is a natural antioxidant that inactivates 5-LO. We demonstrated that esculetin suppresses HSC activation and proliferation in vitro and ameliorates fibrosis in vivo. Hydroxyurea is an anti-cancer drug used to treat melanoma and sickle-cell disease. We showed that hydroxyurea reduces HSC proliferation in vitro and collagen deposition in vivo.
The combination of Hydroxyurea with a 5-LO inhibitor agent, such as melatonin or esculetin, can be a promising drug cocktail that targets various key aspects of HSC activation and leads to regression of liver fibrosis.

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