EXCLI Journal 2020;19:227-229 – ISSN 1611-2156
Received: February 13, 2020, accepted: February 25, 2020, published: February 28, 2020

Letter to the editor:

PPARG AS THERAPEUTIC TARGET FOR ANTIFIBROTIC THERAPY

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http://dx.doi.org/10.17179/excli2020-1136

Dear Editor,

Prevalence and mortality of liver fibrosis continue to grow (Pimpin et al., 2018; Weiskirchen and Tacke, 2016; Leist et al., 2017; Godoy et al., 2013). Liver fibrosis occurs as a consequence of chronic liver damage due to various causes, such as viral infections, super-nutrition, metabolic disorders or genetic diseases (Godoy et al., 2013; Ghallab et al., 2019a).

Recently, Winkler and colleagues performed a comprehensive study to analyze the role of miRNA in liver fibrosis and the development of hepatocellular cancer (Winkler et al., 2020). For this purpose, the authors generated mice that express a constitutively active variant of serum response factor (SRF) in the liver (Winkler et al., 2020). SRF regulates numerous biological processes (Olson and Nordheim 2010; Ohrnberger et al., 2015) and the mice develop hyperproliferative nodules that progress to HCC (Ohrnberger et al., 2015). In this murine HCC model, the authors identified eight miRNA hubs and 54 target genes that regulate components of the fibrotic extracellular matrix (Winkler et al., 2020). Hubs are defined as nodes in a transcriptional regulatory network with an unusual high number of connections (Anastasiadou et al., 2018). Here, the miRNA families let-7, miR-30 as well as miR-29c, miR-335 and miR-338 represent central antifibrotic miRNAs (Winkler et al., 2020). Importantly, these antifibrotic miRNAs (with the exception of miR-335) are regulated by the transcription factor PPARG (Winkler et al., 2020). Therefore, the authors conclude that stimulating this transcription factor may represent a strategy for antifibrotic therapy.

Currently, numerous research activities are performed to identify or optimize therapies for chronic liver disease (Trauner et al., 2017; Svinka et al., 2017; Ghallab et al., 2016; Schliess et al., 2014). A particular challenge are the different etiologies with toxic (Grinberg et al., 2014; 2018; Albrecht et al., 2019; Sezgin et al., 2018), viral (Kazankov et al., 2014; Theise et al., 2018; Maponga et al., 2018), cholestatic (Vartak et al., 2016; Ghallab et al., 2019b; Hessel-Pras et al., 2020) and genetic (Hudert et al., 2019; Jansen et al., 2017) mechanisms. A strength of the present study of Winkler et al. is that the authors have identified hubs to target numerous antifibrotic genes simultaneously, independent of the etiology. Future studies will show, whether hub-targeting therapies will indeed ameliorate fibrosis and delay progression to HCC in mouse tumor models.

Conflict of interest

The authors declare no conflict of interest.

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