Journal of Liver
ISSN: 2167-0889

Niranjan et al., J Liver 2017, 6:3
DOI: 10.4172/2167-0889.1000218

Mini Review Open Access

The Role of MicroRNA-21 and Autophagy in Liver Fibrosis

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Received date: June 30, 2017; **Accepted date:** July 18, 2017; **Published date:** July 20, 2017

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Liver fibrosis is a multifactorial disorder arises primarily due to excessive accumulation of scar and dead tissues that cannot be bio transformed by the liver cells. Fibrosis occurs because of vascular remodelling and several factors are involved in the process [1]. In most of the chronic liver diseases and liver fibrosis, there is significant increase in inflammation and stress followed by vascular remodelling because of extra cellular matrix deposition [2]. Liver injury occurs because of several factors among them the prominent are hepatitis B or hepatitis C virus infections, stress, xenobiotics, alcohol consumption, non-alcoholic steatohepatitis (NASH) [3]. The liver enzymes are unable to degrade scar tissue and the response goes inappropriate and resulting in deposition of more collagen and degradation of elastin in the development of fibrosis [4].

Autophagy is evolutionarily conserved physiological process involved in maintaining the normal functioning of the cells by engulfing the self-organelles and cytoplasmic contents in conditions of nutritional demands [5]. It is initiated during stress and provides an alternate mechanism of intracellular substrate availability for synthesis of larger molecules [6]. Autophagy is involved in tissue remodelling during embryonic development [7]. Involvement of autophagy in the liver fibrosis and other liver diseases is a well-established fact [4,8,9]. However, there is no direct link for miRNA-21 involvement in development of liver fibrosis [10,11]. It's possible that it could play an important role in etiology of the disease by modulating autophagy.

In recent years MicroRNAs (miRNAs) has evolved as one of the major players in understanding the development of human diseases including liver disease. miRNAs are small (21-25 nucleotide) non-coding RNAs that are considered as unique paradigm shifters due to their involvement in most of the physiological processes by regulation of gene at post transcriptional level [12-14]. Studies documented the increased expression of miRNAs such as miR-21 and miR-199 in hepatitis and liver cancer. miR-21 has been shown to promote fibro genesis in muscles and various organs including heart, kidneys, lungs and liver [15]. In liver it induces fibrosis by activating hepatic stellate cells (HSC) [16]. Recently, Ning Zuo-Wei et al. (2017) showed that over expression of mir-21 promotes oxidation, increases in collagen production and to have profound effect on angiotensin activation via Spry1/ERK/NF-κB, Smad7/Smad2/3/NOX4 pathways and its down regulation exerted the opposite effects [16,17]. Our article in PNAS, showed the miR-21 KO mice have reduced tumorigenic activity in multistage murine skin carcinogenesis model [18], indicating down regulation of miRNA could have therapeutic role in cancer therapy [18]. Also another recent study demonstrated the ablation of miR-21 resulted in progressive decrease in steatosis, inflammation and lipoapoptosis with impairment of fibrosis [19]. Similarly, in a different study Kennedy et al. showed the loss of miR-21 expression resulted in decreased collagen deposition and expression of fibrotic markers transforming growth factor-β1 and α-smooth muscle actin in mice model [20]. Further, he demonstrated that human HSCs treated with miR-21 inhibitor in vitro significantly decreased the cell proliferation and expression of fibrotic markers and enhanced the cell apoptosis [20]. The same study linked the increased in Smad-7 expression, decreased biliary hyperplasia and hepatic fibrosis in knocking down miR-21 expression [20].

We conclude that, miR-21 along with autophagy plays major role in liver vascular remodelling and has prominent role in increasing hepatic fibrosis. Thus we propose that modulating miR-21 and autophagy may be a therapeutic option for patients with liver disease and many other diseases in near future.

Acknowledgement

The "young scientist fellowships grant No: SB/YS/LS-198/2014 "(Institutional project No. SERB/BSBE/2016-271)" to Dr. Rituraj Niranjan by SERB (DST, India.) is gratefully acknowledged.

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