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CDKN1A: A double-edged sword in fatty liver?

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Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum, ranging from simple fatty liver, a relatively benign condition, to nonalcoholic steatohepatitis (NASH), characterized by varying degrees of inflammation and fibrosis, with possible progression to cirrhosis and hepatocellular carcinoma (HCC).[1] The pathogenesis is related to adipose tissue insulin resistance, leading to an increased flux of fatty acids to the liver and heightened lipogenesis. Due to the epidemic of obesity, NAFLD is now the most common liver disease, affecting about 30% of the general population, and it is projected to become the leading cause of end-stage disease and HCC within 20 y. However, there is large interindividual variability in the susceptibility to progressive NASH. Although shared environmental triggers such as diet and physical inactivity play a major role, the variation in NAFLD phenotypic expression in persons with similar risk implicates a genetic contribution.[2] In the last few years, the rs738409 C > G polymorphism of PNPLA3 gene, encoding for the I148M protein variant altering lipid metabolism in hepatocytes, has been recognized as the major common determinant of progressive liver disease in NAFLD.[3,4] However, PNPLA3 I148M does not fully explain disease heritability, while genes involved in inflammation, oxidative stress, and fibrogenesis have been implicated in fibrosis progression.[2]

Models of NAFLD reveal also features of accelerated aging, such as impaired liver regeneration and increased HCC risk. During the long-term process of cell death and regeneration in chronic liver injury, telomere shortening in hepatocytes progresses with each cell division. Telomere attrition, as well as DNA damage related to excess generation of reactive oxygen species, result in hepatocellular senescence, which is linked to progressive fibrosis by inducing the proliferation of hepatic stellate cells (HSCs).[5] Critical telomere shortening leads, in turn, to irreversible cell cycle arrest mediated by the cell cycle regulator p21. Expression of p21 is a senescence marker and has been associated with fibrosis stage in NAFLD. Interestingly, previous studies linked variants in p21, encoded by the *CDKN1A* gene, with fibrogenesis in different organs, making plausible the hypothesis that *CDKN1A* might play a similar role in NAFLD.

Within this context, Aravinthan et al. investigated the association between variants of *CDKN1A* and liver damage in 2 cohorts of biopsy-proven NAFLD patients from UK and Finland.[6] Among 6 tagging single nucleotide polymorphisms (SNPs) across *CDKN1A*, rs762623 G > A was linked with fibrosis independently of PNPLA3 I148M and clinical cofactors in UK patients. Furthermore, the association between the rs762623 A allele and fibrosis was replicated in the Finnish cohort and in the combined database. The rs762623 G > A SNP is located in the promoter region of p21 and has been associated with reduced p21 expression by abolishing a E2F transcription factor binding site, and thereby possibly favoring fibrogenesis through reduced HSCs senescence. However, rs762623 seems not to affect fibrosis progression to clinically relevant more severe stages. This may be due to the insufficient study power relative to this outcome, and conclusions are hampered by the lack of prospective assessment. However, as suggested by the authors, it could alternatively be speculated that the initiation and the progression of fibrosis may have a partially different underlying pathophysiology, and that genetic variants might play a role. For example, the *CDKN1A* rs762623 A allele may protect toward advanced fibrosis by reducing senescence in hepatocytes. A working model for the role of p21 in the progression of NAFLD is presented in **Figure 1**.

Clearly, much work has to be done to confirm this hypothesis, but the results by Aravinthan et al.[6] further add to the understanding of the mechanisms underpinning age-related progression of liver disease. As aging, senescence of hepatocytes, and disease progression have been linked in NAFLD, it now becomes important to evaluate the effect of genetic variants regulating cell cycle, telomere length, and senescence on hepatic outcomes. Indeed, anecdotal evidence has already been reported that telomere maintenance genes may influence progression to HCC in NAFLD.[7] Elucidation of the mechanisms linking telomere shortening during aging and chronic high turnover diseases could provide attractive new targets for therapeutic intervention.

References

1. Day CP. Gastroenterology 2006; 130:207-10; PMID:16401483; http://dx.doi.org/10.1053/j.gastro.2005.11.017
2. Dongiovanni P, et al. Curr Pharm Des 2013; 19:5219-38; PMID:23394097; http://dx.doi.org/10.2174/13816128113199990381
3. Romeo S, et al. Nat Genet 2008; 40:1461-5; PMID:18820647; http://dx.doi.org/10.1038/ng.257
4. Valenti L, et al. Hepatology 2010; 51:1209-17; PMID:20373368; http://dx.doi.org/10.1002/hep.23622
5. Aravinthan A, et al. J Hepatol 2013; 58:549-56; PMID:23142622; http://dx.doi.org/10.1016/j.jhep.2012.10.031
6. Aravinthan A, et al. Cell Cycle 2014; 13; PMID:24626178; http://dx.doi.org/10.4161/cc.28471
7. Valenti L, et al. J Hepatol 2013; 58:399-401; PMID:23000435; http://dx.doi.org/10.1016/j.jhep.2012.09.011

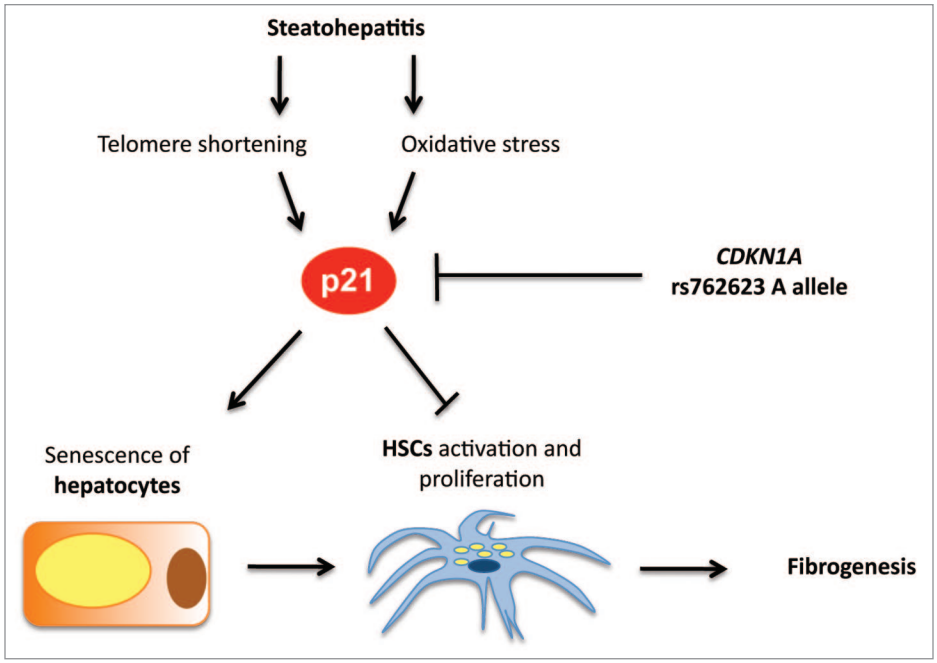

Figure 1. Role of p21 in NAFLD. Telomere shortening/oxidative DNA damage due to steatohepatitis lead to p21 induction. p21 favors senescence, leading to secondary HSCs activation and fibrogenesis, but it also restricts HSCs proliferation limiting fibrogenesis. The *CDKN1A* rs762623 G > A polymorphism favors HSCs proliferation by limiting p21 induction, but it may not predispose to severe fibrosis, because it antagonizes cellular senescence.