Telomere, telomerase, and liver disease

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Telomeres are specialised nucleoprotein complexes located at both ends of each chromosome and maintained by telomerase. Telomerase, first described in 1985 [1], is a complex ribonucleoprotein containing the reverse transcriptase subunit (TERT), the telomerase ribonucleic acid template (TERC), and associated proteins [2]. Telomerase activity is detected readily in cells with high proliferation, characteristically stem cells, germ line cells, and cancer cells. However, telomerase is repressed in most human somatic cells [3, 4], which explains telomere shortening with repeated cell division and in addition, a failure to repair telomeres after direct DNA damage. The loss of telomere integrity independent of telomere length or shortened telomeres induces cellular senescence [5]. Previous studies have demonstrated close links between telomere attrition, cellular senescence and chronic liver disease in man and with non-alcohol-related fatty liver disease in particular [6, 7].

In this issue, Calado and colleagues examined the interaction between critical components of telomerase (TERT and TERC) and a 15-day high fat diet (HFD) in evoking metabolic changes and cell injury in hepatocytes [8]. Using TERT or TERC knockout ($^{-/-}$) murine models, or chemical inhibition of TERT, they demonstrate a highly complex and perhaps unexpected interaction. As anticipated, hepatocyte telomeres were shorter in both TERT$^{-/-}$ and TERC$^{-/-}$ murine models. The 15-day HFD had no impact on hepatocyte telomere length in either knockout model or wild type mice. Hepatocytes from TERT$^{-/-}$ mice showed marked fat accumulation with solid evidence of cell injury; in contrast, hepatocytes from TERC$^{-/-}$ mice were indistinguishable from wild type mice. These data highlight functional differences between TERT and TERC, which appear independent of hepatocyte telomere length and suggest that TERT, but not TERC, is involved in cellular functions unrelated to maintaining telomere length. Both TERT and TERC mutations have been demonstrated in patients with cirrhosis at a higher frequency than in general population [9], so it is uncertain whether the observations in this murine model are also applicable to man, nor is it clear whether the findings in the murine model relate to the duration of the modified diet, leaving the possibility that more prolonged exposure to a HFD would eventually cause comparable fat accumulation and hepatocyte injury in both TERT$^{-/-}$ and TERC$^{-/-}$ mice. The latter possibility is supported by previous evidence wherein TERC$^{-/-}$ mice developed liver dysfunction and cirrhosis following repeated exposure to carbon tetrachloride [10], perhaps a more severe injurious agent than 15-day HFD.

Calado and colleagues then examined the effect of Zidovudine (Azidothymidine [AZT], which inhibits TERT through preferential binding to telomeres) on TERC$^{-/-}$ and wild type mice. In contrast to the TERT$^{-/-}$ model, pharmacological inhibition of TERT in wild type mice did not cause either hepatic fat accumulation or hepatocyte cell injury. TERT inhibition with AZT in TERC$^{-/-}$ mice caused fat accumulation but without any firm evidence of cell injury. These cumulative data suggest that only a complete lack of TERT, as in the TERT$^{-/-}$ model, leads to both fat accumulation and hepatocyte

injury after 15-day HFD and that the presence of TERT, even at reduced levels (as with dose-dependent AZT inhibition of TERT [11]) may prevent hepatocyte injury. The study is compromised by the short duration of exposure to a HFD. It is otherwise an appealing target for therapeutic intervention, but only after more rigorous study.

While these data demonstrate a clear role for both TERT and TERC in the evolution of liver injury, it is important to highlight that the relation between telomere length and liver disease is bi-directional. Just as genetic telomere defects and telomerase deficiency predispose to liver injury [10, 12], chronic hepatocyte injury causes telomere shortening through DNA damage [6, 7, 13]. Correction of genetic telomere or telomerase defects may alleviate liver dysfunction, even after the development of advanced liver disease [10], but there is no evidence that these approaches would benefit patients with liver disease when telomere erosion is a direct consequence of repetitive or persistent hepatocyte injury.

The incidence of non-alcoholic fatty liver disease (NAFLD) is high in those infected with the human immunodeficiency virus (HIV) and around half of those with liver blood test abnormalities that cannot be attributed to concurrent hepatitis B or hepatitis C virus co-infections are thought to have steatohepatitis [14]. In addition to well recognised risk factors for NAFLD, the prolonged use of TERT inhibitors such as AZT and Tenofovir, has been shown to be an independent risk factor for NAFLD [15, 16]. The murine study described by Calado and colleagues provide a rational explanation for the association between anti-retroviral treatment of HIV and NAFLD, and support a potential role for TERT in hepatic steatosis and hepatocyte injury, while raising important issues regarding drug-induced cellular senescence [17] and accelerated ageing [18-20] in HIV-infection. A similar scenario may occur with sustained antiviral therapy for hepatitis B virus infection using Tenofovir.

It is important to highlight that both $TERT^{-/-}$ and $TERC^{-/-}$ models described by Calado and colleagues were global knockouts, thus affecting all organs; hepatocyte-specific knockouts would have been a stronger approach. So, it is not unreasonable to assume that immune senescence would have been integral to their model and may have played some part in the various manifestations of liver disease described. Immune senescence has been demonstrated in type-2 diabetes mellitus, which has a strong association with the development of fatty liver disease [21] and impaired clearance of senescent hepatocytes by immune cells (known as senescence surveillance) contributes to the development of hepatocellular carcinoma arising from senescent hepatocytes [22].

In conclusion, the current study by Calado and colleagues sheds some light on the influence of both TERT and TERC in the early phases of liver disease, but as with all research also generates more complex questions. The interaction between telomeres, telomerase, and hepatocyte injury is a multi-level process and more detailed understanding may help develop newer therapeutic strategies.

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