Telomerase gene mutations are associated with cirrhosis formation.

Abstract:
Telomere shortening impairs liver regeneration in mice and is associated with cirrhosis formation in humans with chronic liver disease. In humans, telomerase mutations have been associated with familial diseases leading to bone marrow failure or lung fibrosis. It is currently unknown whether telomerase mutations associate with cirrhosis induced by chronic liver disease. The telomerase RNA component (TERC) and the telomerase reverse transcriptase (TERT) were sequenced in 1,121 individuals (521 patients with cirrhosis induced by chronic liver disease and 600 noncirrhosis controls). Telomere length was analyzed in patients carrying telomerase gene mutations. Functional defects of telomerase gene mutations were investigated in primary human fibroblasts and patient-derived lymphocytes. An increased incidence of telomerase mutations was detected in cirrhosis patients (allele frequency 0.017) compared to noncirrhosis controls (0.003, P value 0.0007; relative risk [RR] 1.859; 95% confidence interval [CI] 1.552-2.227). Cirrhosis patients with TERT mutations showed shortened telomeres in white blood cells.
compared to control patients. Cirrhosis-associated telomerase mutations led to reduced telomerase activity and defects in maintaining telomere length and the replicative potential of primary cells in culture. CONCLUSION: This study provides the first experimental evidence that telomerase gene mutations are present in patients developing cirrhosis as a consequence of chronic liver disease. These data support the concept that telomere shortening can represent a causal factor impairing liver regeneration and accelerating cirrhosis formation in response to chronic liver disease.