FEATURES

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Transplantation of hepatocytes is a promising therapy for end-stage liver disease, but the availability of functional cells currently precludes its clinical application. We now report a simple transient reprogramming approach to convert fibroblasts into hepatic-like cells. Human skin fibroblasts were treated with fish egg extracts to become the transiently remodeled cells (TRCs). After infected with retroviral EGFP, they were directly injected into the fetal monkey liver, where they underwent in situ differentiation in the hepatic niche. The hepatic-like cells were functional as shown by the synthesis of hepatic markers in vivo, including albumin, cytokeratin-18, and hepatic serum antigen. Similarly, when implanted in the mouse liver, the TRCs were differentiated into hepatic-like cells that synthesize albumin and CK18 and became completely integrated into the liver parenchyma. The potency of TRCs was mechanistically related to the activation of several signal pathways, which reactivate endogenous genes related to cell potency. This study demonstrates the feasibility of a simple and inexpensive epigenetic remodeling approach to convert human fibroblasts into therapeutic hepatic-like cells for the treatment of end-stage liver disease.

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TCERG1 was characterized previously as a repressor of the transcription factor C/EBPα through a mechanism that involved relocalization of TCERG1 from nuclear speckles to pericentromeric regions. The inhibitory activity as well as the relocalization activity has been demonstrated to lie in the amino terminal half of the protein, which contains several discrete motifs including an imperfect glutamine-alanine (QA) repeat. In the present study, we showed that deletion of this domain completely abrogated the ability of TCERG1 to inhibit the growth arrest activity of C/EBPα. Moreover, the QA repeat deletion mutant of TCERG1 lost the ability to be relocalized from nuclear speckles to pericentromeric regions, and caused an increase in the average size of individual speckles. We also showed that deletion of the QA repeat abrogated the complex formation between TCERG1 and C/EBPα. Examination of mutants with varying numbers of QA repeats indicated that a minimal number of repeats are required for inhibitory activity as well as relocalization ability. These data contribute to our overall understanding of how TCERG1 can have gene-specific effects in addition to its more general roles in coordinating transcription elongation and splicing.