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Oncogenic NELFE Enhances MYC-induced Hepatocellular Carcinogenesis

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Transcriptomic alterations of MYC targets are associated with human cancers, including hepatocellular carcinoma (HCC**).** RNA binding proteins (RBPs), key regulators of RNA processing, can mediate cancer-associated transcriptomic changes often observed in HCC. In this study, we investigated the oncogenic role of the RBP Negative elongation factor E (NELFE) in HCC. NELFE mRNA is significantly elevated in HCC, which is attributed by increased gene copy number alterations. Moreover, increased NELFE gene copy is associated with poor survival. We show that oncogenic activation of NELFE promotes HCC progression by enhancing MYC signaling in two ways: 1) NELFE can directly interact with the 3'UTR of MYC target mRNAs to affect RNA stability or 2) through protein-protein interactions where NELFE modulates MYC binding to its target gene promoter regions to enhance transcription. Moreover, the overexpression of NELFE in MYC-induced HCC *Trp53*$^{flox/flox}$;alb-cre mouse models enhanced HCC progression. We thus exploited this interplay by performing survival risk prediction analysis to develop a 20-NELFE dependent MYC target (NDMT) gene signature. This signature identified two distinctive subclasses associated with overall survival. In addition, independent cross-validation in four independent cohorts of more than 900 HCC samples demonstrate that the 20-NDMT signature is robust and predictive independently of clinical characteristics. In addition, high risk patients who have undergone transarterial chemoembolization (TACE) has a worse prognosis and increased recurrence. Together, our results suggest that oncogenic activation of NELFE supports a transcriptomic imbalance that promotes HCC progression.