Transcriptomic analysis of human liver identifies a novel class of regulatory RNAs in chronic viral hepatitis and associated cancer

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Abstract. Hepatitis B and C viruses infect millions of people worldwide and may result in chronic liver disease leading to hepatocellular carcinoma (HCC). To profile the entire small RNA transcriptome in chronic viral hepatitis, we performed Illumina deep sequencing of small RNAs in matched tumor and non-tumor liver tissue from eight a ge-matched Japanese m ale patients with v iral-hepatitis induced H CC (four chronic HBV and four chronic HCV). We also sequenced liver tissue from four uninfected J apanese male p atients as well as a widely-used h uman h epatoma cellline (Huh7). In each dataset, a considerable proportion of the reads were of length 20-24 nucleotides, which is the expected size of microRNAs (miRNAs). Surprisingly, in the non-tumor tissue from patients with chronic HBV or HCV, we also detected an abundance of reads of length 32-35 nucleotides. This spike in the read length distribution was substantially less pronounced in matched tu mor tis sue from in fected p atients, liver tissue from uninfected patients, and Huh7 cells. We aligned the sequences in the 32-35 nucleotide size range to the human genome and found that all of them mapped to an notated t ransfer R NA (tRNA) genes. The v ast majority of the t RNA-derived reads correspond to the region from the 5'-most position of the tRNA to the anticodon triplet. F urthermore, these RNAs, which we refer to as 5' tRNA-halves, are more abundant than miRNAs in the non-tumor liver tissue from infected patients. We repeated t hese t ranscriptomic analyses in c himpanzee a nd mouse l ivers c hronically infected with HBV and ag ain o bserved a s ignificant increase in tRNA halves. We validated the deep sequencing results by real time quantitative PCR for the most highly abundant tRNA halves and also performed preliminary functional analyses, which indicate that tRNA halves may be involved in the regulation of mRNA translation under stress conditions. To our knowledge, this is the first time that tRNA-derived RNAs have been discovered in primary human tissue.