Inhibition of HCV replication and IRES-dependent translation by an RNA molecule.

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Hepatitis C virus (HCV) protein synthesis is mediated by a highly conserved internal ribosome entry site (IRES), mostly located at the 5' untranslatable region (5'UTR) of the viral genome. The translation mechanism is different from that used by cellular cap-mRNAs, making IRES an attractive target site for new antiviral drugs. The present work characterizes a chimeric RNA molecule (HH363-50) composed of two inhibitors: a hammerhead ribozyme targeting position 363 of the HCV genome, and an aptamer directed towards the essential stem-loop structure in domain IV of the IRES region (which contains the translation start codon). The inhibitor RNA interferes with the formation of a translationally active complex, stalling its progression at the level of 80S particle formation. This action is likely related to the effective and specific blocking of HCV IRES-dependent translation achieved in Huh-7 cells. The inhibitor HH363-50 also reduces HCV RNA levels in a subgenomic replicon system. The present findings suggest that HH363-50 could be an effective anti-HCV compound and highlight the possibilities of antiviral agents based on RNA molecules.

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