Inhibition of SARS-associated coronvirus infection and replication by siRNA

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A novel coronavirus has been identified as the etiologic agent of the recent worldwide outbreak of severe acute respiratory syndrome (SARS). Drug development for the treatment of SARS is urgently needed. Small interfering RNA (siRNA) is a double-stranded RNA (dsRNA) that directs the sequence-specific degradation of messenger RNA in mammalian cells. This offers the possibility of developing a new anti-viral therapy for SARS. Based on the complete coronavirus genomic sequence and the functional domains, we have designed six siRNAs targeting the replicase region of the virus. Here we describe the inhibition of coronavirus infection and replication by the synthetic 21- and 22-mer siRNAs.

We designed six 21-mer siRNAs targeting different sites of the SARS-CoV replicase 1A. The anti-SARS-CoV activities of these siRNAs were tested in monkey kidney cells (FRhk-4 cells). FRhk-4 cells were transfected with siRNAs, and then infected with one isolate of SARS-CoV. As compared to the uninfected cells, cells infected with SARS-CoV exhibited a marked morphological change with CPE. Sarsi-2, sarsi-3 and sarsi-4 markedly inhibited the CPE caused by viral infection and replication , whereas sarsi-1, sarsi-5 and sarsi-6 were less effective judged by morphological changes. The results were further confirmed by immunostaining with antibody against SARS-CoV antigens. Consistently, the viral titers as determined by quantitative RT-PCR were reduced 92.5%, 89.6% and 85.8% by sarsi-4, sarsi-2, and sarsi-3, respectively, but only 50% to 65% by the other three siRNAs. Furthermore, the effective sarsi-2,3,4 also inhibited the infection and replication of other different strains of SARS-CoV isolates.