Retrovirology

Poster presentation

P19-22. CD4-targeted delivery of HIV and CCR5 siRNAs by aptamer-siRNA chimeras suppresses HIV infection in primary cells and in human cervical explants

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Background

The therapeutic use of small interfering RNAs (siRNA) to prevent or treat HIV infection requires an effective means for *in vivo* delivery into susceptible target cells. Transfection of lymphocytes is especially difficult, even *in vitro*. Aptamers, which are small structured nucleic acid sequences that bind with high specificity to individual proteins, provide an attractive approach for cell-specific targeting.

Methods

We designed a chimeric RNA, which was transcribed *in vitro*. It was composed of a CD4-specific aptamer fused to the 21 nucleotide passenger siRNA strand, and then complexed with the complementary 21 nucleotide active siRNA strand. We hypothesized that the partially-duplexed RNA would be selectively internalized into CD4+ cells following receptor binding to the aptamer, and would be subsequently processed by Dicer into an active siRNA capable of knocking down target genes.

Results

Specific delivery and knockdown was first evaluated by comparing lamin expression, measured by RT-PCR and Western blot, in HeLa cells stably transfected to express CD4 or control CD4- HeLa cells treated with CD4 aptamer-lamin siRNA chimeras. Lamin gene silencing was observed in CD4+ HeLa cells, but not in CD4- HeLa cells, and required both the CD4-aptamer and the lamin siRNA. Similarly, lamin expression was knocked down in primary CD4+ T-cells and macrophages. To investigate whether this system could be used to suppress HIV infection, CD4-aptamer chimeras were designed to encode siRNAs targeting the viral genes gag, vif and the HIV co-receptor, CCR5. Anti-HIV RNAs, alone and in combination, inhibited HIV infection, as monitored by intracellular p24 staining and p24 ELISA, in primary macrophages and CD4+ T-cells by 70–90%. Preliminary data also suggest efficient inhibition of HIV transmission to polarized human cervical explants.

Conclusion

These findings suggest that siRNA-aptamer chimeric RNAs could be an effective, cell-type specific therapeutic gene silencing approach to prevent HIV transmission or treat HIV infection.