Anti Viral Treatments-siRNA

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Anti Viral Chemotherapeutic Agents

- A successful anti-viral drug should:

  (i) interfere with a virus-specific function (either because the function is unique to the virus or the similar host function is much less susceptible to the drug)

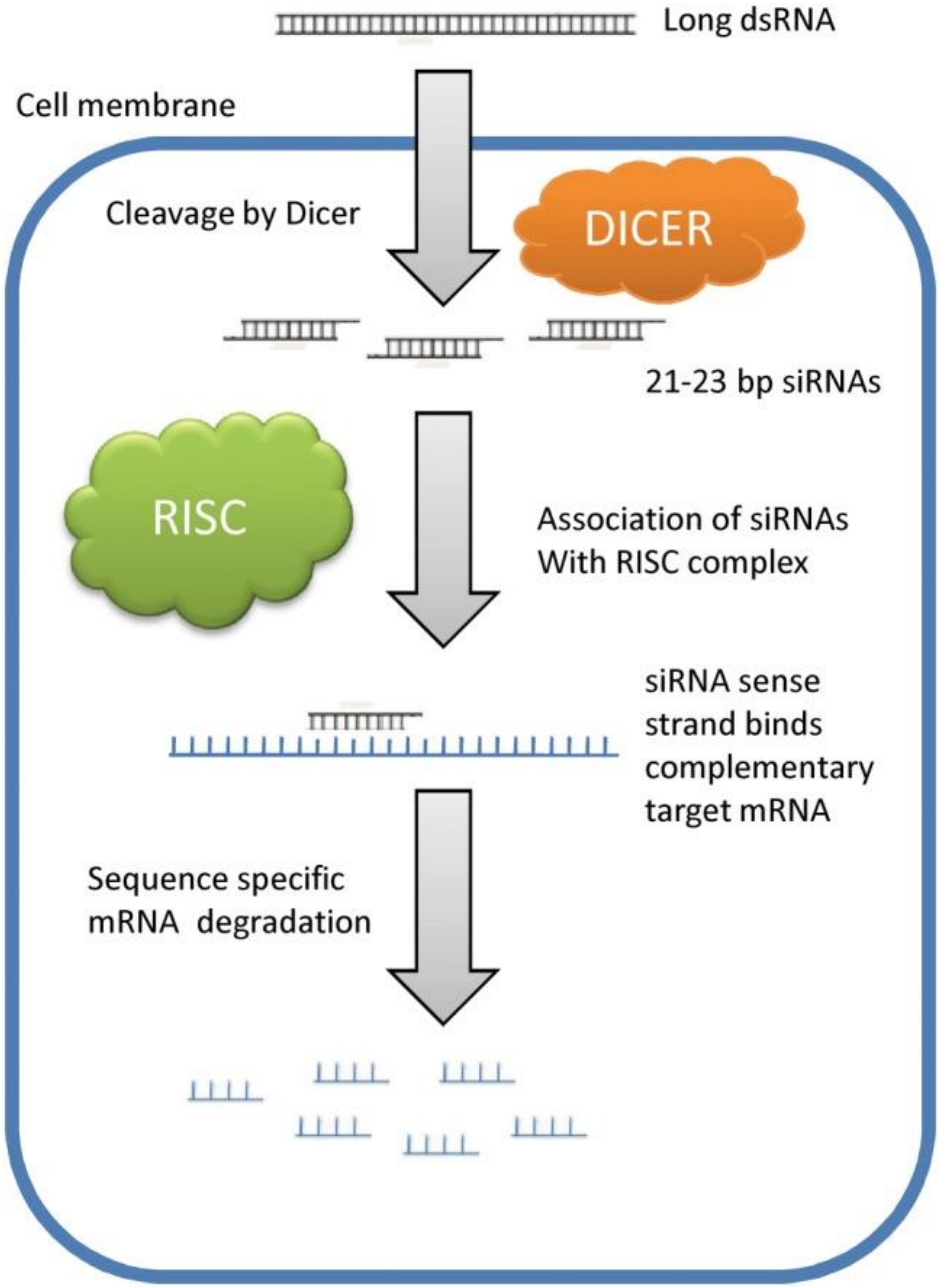
  (ii) interfere with a cellular function so that the virus cannot replicate.
- To be specific, the anti-viral drug must only kill virus-infected cells.

si RNA as antiviral agent

- 1988. Fire and Mello discover RNAi in *C. elegans*
- 1996. Fire and Mello Nobel Prize for siRNA discovery
- Short interfering RNA of silencing RNA is a class of double stranded RNA molecules about 20-25 bp
- RNA interference is biological process wherein RNA molecules inhibit gene expression of target protein by causing degradation of specific mRNA molecules
- Binds with complimentary strand of RNA and interferes with gene expression by degrading mRNA
- Protect against viral infection

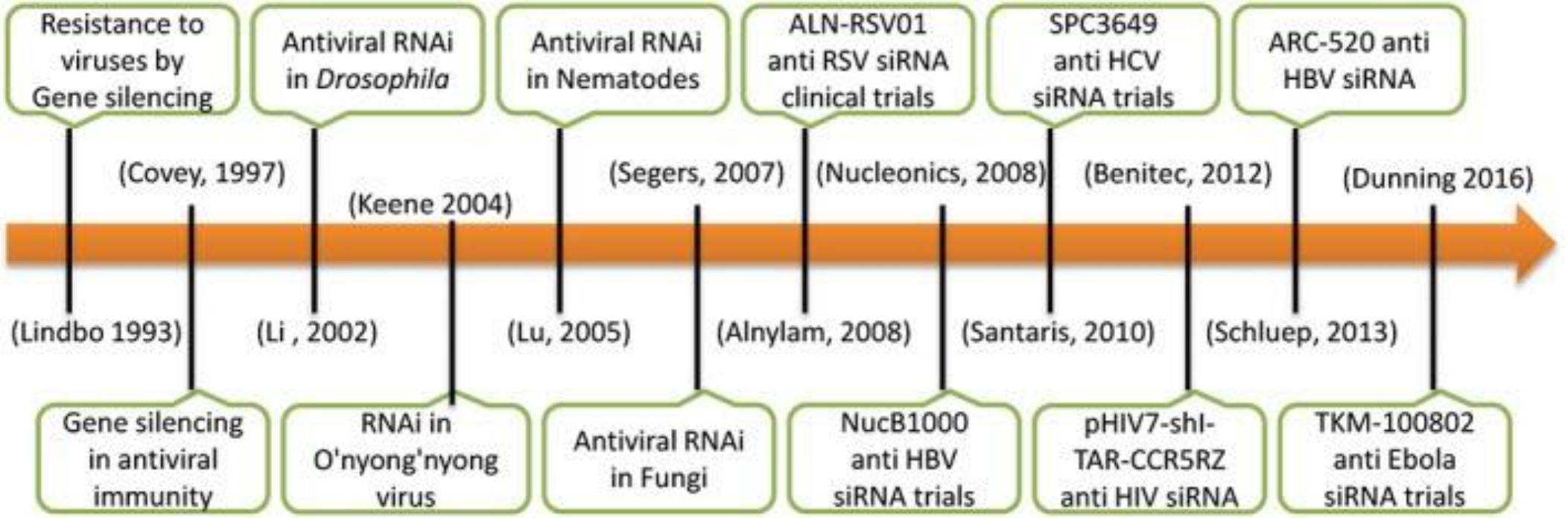
RNAi Pathway

- The RNAi silencing pathway involves chopping of dsRNA into siRNA by enzyme DICER (RNAse type III family) that are typically 21 to 25 base pairs long dsRNA having dinucleotide overhangs on the 3′ termini.
- One of the siRNA strands (guide strand) is then incorporated into an RNA-induced silencing complex (RISC) that degrades the target mRNA.



Qureshi A, Tantray VG, Kirmani AR, Ahangar AG. A review on current status of antiviral siRNA. Rev Med Virol. 2018 Jul;28(4):e1976. doi: 10.1002/rmv.1976.

Short interfering RNAs can be used against all types of viral genomes, be it double- or single-stranded DNA/RNA



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si RNA in clinical trials

Virus				
Respiratory Syncytial Virus	ALN-RSV-01	Targetd to nucleocapsid gene	Naked siRNA	Intranasal
Hepatitis B Virus	NUC B1000	Targeted to polymerase geen and HBsAG gene	Plasmid DNA in cationic lipid	i/v
	ARC-521	2siRNA targeted to integrated viral genome		i/v
HIV -1	LVsh5/C46- Cal1	Downregulate CCR5 and Hiv fusion inhibitor	Lentivirus vector on HIC backbone	Induced in stem cells of CD4 T cells
Hepatitis C Virus	TT-034	Adenovirus vector 8	Liquid nanoparticles	i/n

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Methods of siRNA preparation

- Chemical Preparation
- Enzymatic Production:has been based on *in vitro* transcription of DNA templates containing T7 polymerase promoter. A diverse siRNA pool derived from a long fragment of viral genome, which mimics the natural RNAi-based antiviral defense, is more protective than a single-site siRNA.
- In vivo expression from SiRNA expression cassette or vector:Dicer cleavage of small hairpin RNA (shRNA) transcribed in a cell from an expression cassette containing a polymerase III promoter (U6 or H1), a DNA template of desired shRNA sequence, and transcription stop signal Expression cassette integrated into plasmid or viral vector

Summary

- siRNAs can effectively inhibit the replication of various viruses
- unresolved issues with safe and efficient delivery of siRNAs to the target tissues and cells
- Resistance due to Interferon pathway-disadvantage

Reference