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Unit – IV

TOPIC: Mechanism of action and clinical application of antisense oligonucleotides

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Mechanism of action and clinical application of antisense oligonucleotides

Antisense oligonucleotides

- Antisense oligonucleotides (ASOs) are short, synthetic, single-stranded nucleic acids (either DNA or RNA) designed to specifically bind to complementary sequences of RNA.
- By binding to their target RNA, ASOs can modulate gene expression in several ways, such as degrading the RNA, altering splicing patterns, or blocking the translation of the RNA into protein.
- These mechanisms make ASOs powerful tools for research and therapeutic applications, particularly in targeting genetic diseases.

How does ASO Work?

1. Binding to mRNA:

   ASOs bind through Watson-Crick base pairing.

2. Modulation of Gene Expression:

   Can lead to degradation of mRNA, alteration of splicing, or inhibition of translation.

Mechanism 1
RNAse H-Mediated Degradation

RNAse H Activation

- ASOs hybridize with target mRNA, forming an RNA-DNA duplex.
- RNAse H, a ribonuclease enzyme, recognizes the duplex and cleaves the RNA strand.

- Result

  mRNA degradation and reduction of the corresponding protein.

Mechanism 2
Steric Blockage

Inhibition of Translation:

ASOs bind to mRNA without inducing degradation.

This can block the ribosome from translating the mRNA.

Result

Inhibition of protein synthesis.

Mechanism 3
Splice Modulation

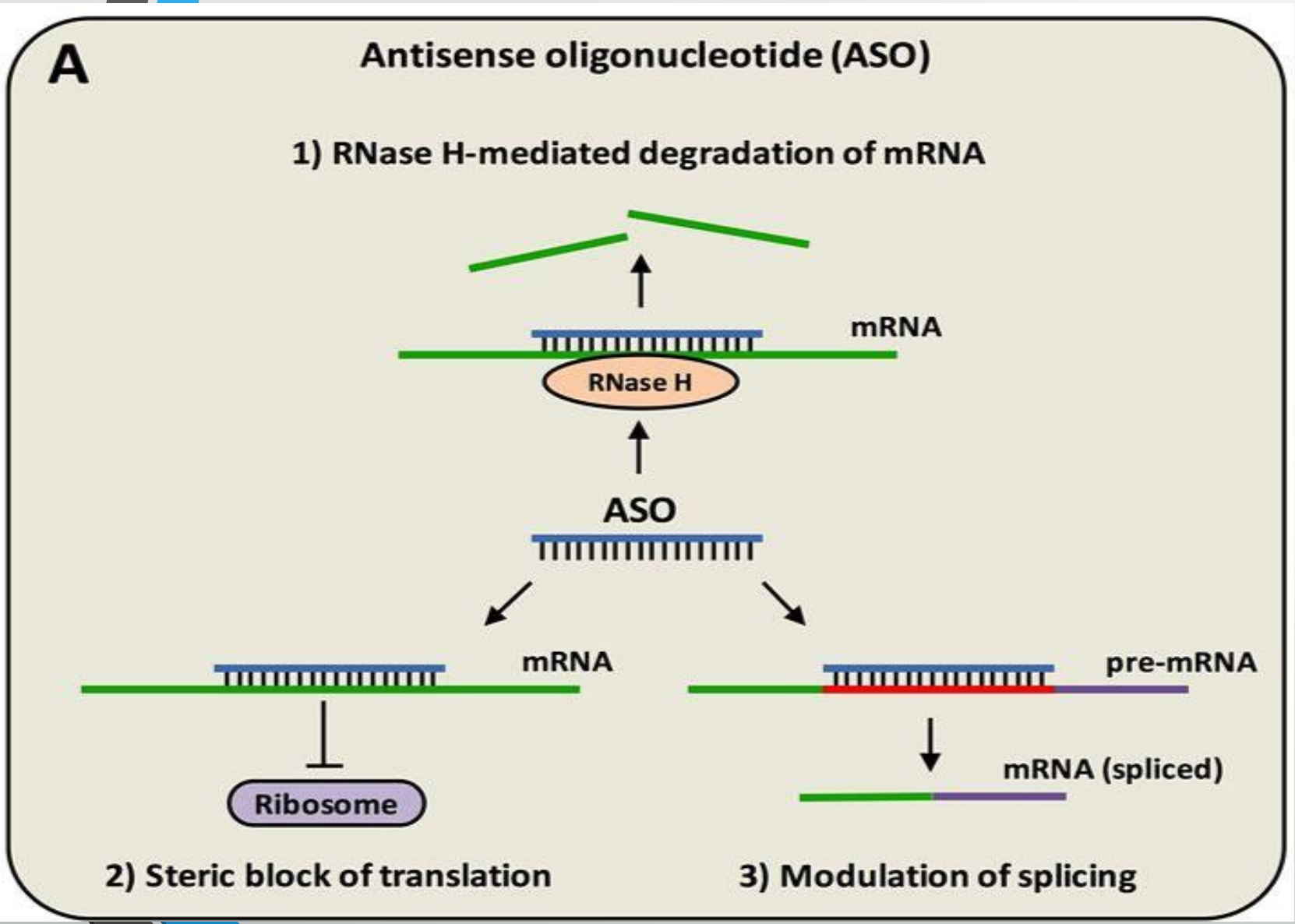
Alteration of Splicing Events

ASOs bind to pre-mRNA at splice sites or regulatory sequences.

This can block splicing machinery, leading to exon skipping or inclusion.

Result

Production of a different protein isoform or reduction of a harmful variant.



The figure shows the diagrammatic representation of the mechanism of action of ASO

1. RNAse H-Mediated Degradation
2. Steric blockage
3. Splice modulation

Advantages of ASO

1. Target Specificity

   High specificity for mRNA sequences.

2. Versatility

   Can be designed for a wide range of genes.

3. Potential to Treat Genetic Diseases

   Particularly useful in cases where traditional drugs are ineffective.

Challenges and Limitations

- Delivery Issues

  Ensuring ASOs reach target tissues effectively.

- Stability

  ASOs must be chemically modified to resist degradation.

- Off-Target Effects

  Potential for unintended interactions with non-target RNAs.

Examples of FDA-Approved ASO Drugs

1. Nusinersen (Spinraza)

   Treats Spinal Muscular Atrophy by modifying SMN2 mRNA splicing.

2. Eteplirsen (Exondys 51)

   Induces exon skipping in Duchenne Muscular Dystrophy.

3. Mipomersen (Kynamro)

   Lowers cholesterol by targeting APOB mRNA.

Therapeutic Applications

Genetic Disorders:

- Spinal Muscular Atrophy (SMA): Nusinersen (Spinraza) increases functional SMN protein production.
- Duchenne Muscular Dystrophy (DMD): Eteplirsen enables the production of a functional dystrophin protein.
- Cancer Treatment: Targeting oncogenes to reduce cancer cell growth.
- Viral Infections: ASOs can target viral RNA (e.g., HIV, Hepatitis C) to prevent replication.

Future Directions

- Improved Delivery Methods: Use of nanoparticles, chemical modifications, and viral vectors.
- Broader Applications: Potential for treating neurodegenerative disorders and other complex diseases.
- Combination with Gene Editing: Enhancing precision in gene regulation.

References

- Metabolism of Oligonucleotides – by R. M. Crooke
- Pharmacological Effects of Antisense Oligonucleotide Inhibition of Immediate-Early Response Genes in the CNS B. J. Chiasson, M. O. Hebb, H. A. Robertson
- Use of Antisense Oligonucleotides to Modify Inflammatory Processes C. F. Bennett, T. P. Condon

Thank you