NATURAL mRNA EDITING – SCIENCE & TECHNOLOGY

NEWS: Recently, a Chinese study reveals that A-to-I mRNA editing is developmentally regulated in fungi, yet its evolutionary purpose remains unclear.

WHAT'S IN THE NEWS?

What is mRNA Editing?

- Definition: mRNA editing is a post-transcriptional modification process where messenger RNA (mRNA), after being transcribed from DNA, is enzymatically altered before translation into proteins.
- Key Function: This process allows the nucleotide sequence of mRNA to be changed, thus potentially altering the amino acid sequence of the resulting protein without modifying the original DNA.

A-to-I mRNA Editing Mechanism

- Enzyme Involved: The conversion is carried out by ADAR proteins (Adenosine Deaminases Acting on RNA).
- Editing Process: ADAR enzymes convert adenosine (A) to inosine (I) in the RNA strand.
- Ribosomal Interpretation: The cellular ribosome reads inosine as guanine (G), leading to a change in the codon and thus the protein product.
- Functional Outcome: This editing mechanism can result in functionally different protein isoforms from the same gene sequence.

Purpose and Functional Significance

- Biological Flexibility: A single gene can give rise to multiple protein variants, enabling organisms to adapt to different physiological or environmental conditions.
- No DNA Alteration: The original DNA blueprint remains unchanged, preserving genomic integrity while allowing temporary protein modifications.

Complications and Risks of mRNA Editing

- Override of Natural Stop Codons: In some cases, editing can convert stop codons (e.g., UAG to UGG), leading to elongated proteins.
- Functional Risks: These extended proteins may lose normal function or gain toxic effects, potentially leading to cellular dysfunction or disease.
- Evolutionary Concerns:
    - Scientists question the necessity of such a complex mechanism.

    - Simpler DNA-based mutations could theoretically produce similar outcomes, raising debate on the evolutionary advantage of RNA editing.

Natural Role of mRNA Editing in Fungi: The Case of Fusarium graminearum

- Lifecycle-Specific Editing: Research reveals that A-to-I editing in F. graminearum is stage-specific:
    - No editing during vegetative growth, leaving certain genes inactive.
    - High editing during the sexual reproduction stage, activating over 26,000 editing sites.
- Activation of PSC Genes:
    - Identified 71 PSC (Premature Stop Codon) genes that are only activated via editing during the sexual stage.
    - Editing removes premature stop signals, allowing full-length, functional protein production.
- Functional Importance:
    - Deletion of PSC genes impairs sexual development, proving their critical role.
    - Two specific genes, PSC64 and PSC69, are conserved during asexual growth and help the fungus cope with environmental stress.
- Evolutionary Insight: Permanent replacement of stop codons in DNA would eliminate lifecycle adaptability, proving that RNA editing preserves genetic flexibility.

Broader Biological Perspective: DNA–RNA–Protein Paradigm

- Central Dogma: DNA is the genetic instruction manual; mRNA carries specific instructions to ribosomes, which assemble proteins from amino acids.
- RNA Editing as Regulation: Through ADAR-mediated editing, organisms can fine-tune protein expression without permanent genetic changes, adapting to temporary physiological needs.

Outstanding Scientific Questions

- Widespread Editing, Limited Benefits:
    - Although thousands of mRNA sites undergo A-to-I editing, only a few have known functional benefits.
    - The full biological rationale behind the extensive use of this mechanism remains unclear and under research.

Technological and Medical Applications

A. mRNA Vaccines

- COVID-19 Example: Vaccines like those for COVID-19 use synthetic mRNA to instruct human cells to produce viral proteins that trigger an immune response.
- Safe and Non-Permanent: Since mRNA doesn't integrate into DNA, it is transient and safer for use.

B. Gene Therapy

- Somatic Gene Therapy: Modified mRNAs can be used to correct faulty proteins in somatic (non-reproductive) cells without changing the DNA.
- Future Potential: Controlled RNA editing could allow precise protein regulation for diseases caused by dysfunctional proteins.

Conclusion

- Scientific Significance: mRNA editing represents a powerful tool for increasing genetic and functional diversity without altering DNA.
- Biotechnological Potential: Its expanding use in vaccines, therapeutics, and precision medicine showcases its utility.
- Research Frontiers: Despite its promise, the evolutionary role and full functional benefits of widespread RNA editing remain to be fully understood.

Source: https://www.thehindu.com/sci-tech/science/our-bodies-perform-a-kind-of-mrna-editing-and-we-dont-know-why/article69423396.ece