Int. J. Pharm. Investigation, 2026; 16(2):517-522.
https://www.jpionline.org

Review Article

Metabolism of mRNA Therapeutics: Insights into Pharmacokinetics and Toxicology

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ABSTRACT

Messenger RNA (mRNA) therapies are a groundbreaking treatment for various conditions, including infectious diseases, cancer, and genetic disorders. This review examines the processing of mRNA therapeutics in the body, focusing on pharmacokinetics, cellular handling, and potential toxicity. It highlights the importance of delivery methods, immune responses, and mRNA stability for effective treatment. Additionally, it addresses challenges like unintended effects and long-term safety, while proposing strategies to enhance mRNA stability and reduce toxicity. Ultimately, it provides insights into how understanding mRNA metabolism can support the future development of these therapies.

Keywords: mRNA therapeutics, Pharmacokinetics, Immune responses, Stability, Toxicity.

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Received: 09-08-2025;
Revised: 28-10-2025;
Accepted: 14-12-2025.

INTRODUCTION

mRNA therapies are transforming healthcare by enabling cells to produce disease-fighting proteins. Unlike traditional medications, they allow the body to generate therapeutic proteins useful for vaccines, cancer treatment, and genetic disorders. COVID-19 vaccines use mRNA to trigger immune responses, while in cancer, mRNA targets tumor antigens, and for genetic conditions, it aids in restoring essential proteins. Understanding the absorption, distribution, metabolism, and elimination of mRNA is vital for ensuring its safety and effectiveness (Karikó *et al*., 2008).

mRNA metabolism: an overview

mRNA consists of key components: the 5′ cap, UTRs, ORF, and poly(A) tail, which affect its stability, translation, and which influence its stability, translation efficiency, and therapeutic use, as illustrated in Figure 1 (Mockey 2006; Henderson 2021; Grier 2016). The 5′cap, a modified guanine, prevents degradation and aids translation; improved analogs can enhance capping efficiency to 95%, boosting stability and protein production, as demonstrated in Figure 2. The poly(A) tail, consisting of approximately 100–300 adenine residues, also increases stability and can be optimized for better performance (Holtkamp 2006; Schlake 2012). UTRs regulate translation and can be tailored for better efficiency and tissue-specific expression. While many mRNAs use α- or β-globin UTRs, further optimization can increase yield (Holtkamp 2006; Vaidyanathan 2018; Ross and Sullivan, 1985).

Modified nucleosides such as 1-methylpseudouridine and N1-methyladenosine boost mRNA stability and lower immune activation. N1-methyladenosine aids in evading RIG-I, which enhances delivery and diminishes the immune response-crucial for progressing mRNA therapies for infections, cancer, and genetic disorders (Pascolo 2021; Sahin *et al*., 2014; Kowalski 2019).

Degradation pathways

Endogenous enzymes control mRNA stability and degradation. Deadenylases shorten the poly(A) tail to start decay, while decapping enzymes DCP1 and DCP2 remove the 5' cap, resulting in degradation by the exosome complex, represented in Figure 3 (Karikó 2011). Eukaryotic mRNAs degrade from the 3' to 5' end after the poly(A) tail is removed, which is crucial for mRNA stability and translation (Muhlrad *et al*., 1994; Muhlrad *et al*., 1995).

In yeast, blocking 5' to 3' decay causes accumulation of 3' PGK1 mRNA fragments, suggesting a shift to 3' to 5' decay. Similar results in oat phytochrome A mRNA indicate this process is conserved (Higgs and Colbert, 1994). The exact roles of exonucleases and endonucleases remain unclear. Notably, some mRNAs display

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DOI: 10.5530/ijpi.20260539

stability without a poly(A) tail, indicating that other factors contribute to stability (Decker and Parker, 1993; Dujon, 1994).

Pharmacokinetics of mRNA therapeutics

Delivery systems and tissue targeting

mRNA delivery efficiency is greatly influenced by the method used, with Lipid Nanoparticles (LNPs) being the most common. LNPs enter cells via endocytosis, releasing mRNA for protein synthesis. Advanced systems like polymeric and hybrid lipid-polymer nanoparticles enhance targeting, while polymeric carriers show promise for lung treatments in asthma and COPD (Hou 2021; Riley, 2021).

Modern RNA-loaded Lipid Nanoparticles (LNPs), evolved from 1960s liposomes, consist of cholesterol, ionizable lipids, and stealth lipids. Their core features structural lipids, while neutral phospholipids stabilize the bilayer and cholesterol enhances RNA delivery efficiency (Riley 2021; Ad, 1965; Briuglia, 2015; Gregoriadis and Davis, 1979; Kirby *et al*., 1980; Malone *et al*., 1989).

Stability and protein translation

mRNA stability is crucial for its longevity and protein production, especially in therapies. Innovations like Clean Cap, a 5' cap analog, enhance stability, translation efficiency, and degradation resistance, leading to a longer half-life and increased protein synthesis (Wu 2024; Rouf, 2022). Modifying UTRs boosts stability, aiding single-dose vaccines like Zika by enhancing immune responses and reducing dosage (Richner, 2017; Hengelbrock, 2023). PERSIST-seq involves introducing mRNA pools into HEK293T cells, separating translating from non-translating mRNAs with sucrose gradients. RT-PCR and Illumina sequencing assess translation efficiency, with polysome-associated mRNAs indicating active translation (Kozak, 1994; Babendure, 2006). Early results showed clear translation differences between ActB mRNA and scrambled UTR controls (Osuna, 2017).

Clearance pathways

Post-translation, mRNA breaks down into nucleotides, regulating gene expression and preventing protein accumulation. These nucleotides can be reused or converted into essential metabolites, with excess eliminated to maintain balance (Hoecke and Roose, 2019; Stephenson and Zamecnik, 1978). Clearance mainly involves the kidneys and liver. The kidneys filter waste and salts into urine, while the liver transforms substances into less harmful or water-soluble forms (Sharma and Watts, 2015; Dammes and Peer, 2020; Holland 2024). The liver produces proteins, regulates glucose storage, and secretes bile for fat digestion, all vital for drug development (Holland, 2024). Understanding nucleotide metabolism aids drug optimization, improving efficacy and safety by balancing clearance rates to reduce dosing frequency and toxicity, while enhancing stability and bioavailability (Watson and Crick, 1953).

Toxicological implications

Immunogenic responses

Unaltered mRNA activates receptors like TLR3, TLR7, TLR8, and RIG-I, causing inflammation or autoimmune responses. Modified nucleosides, such as 5-methylcytidine and pseudouridine, enhance stability, reduce immune detection, and improve translation (Moles 2019; Mu and Hur, 2021). Enhanced delivery boosts safety and effectiveness in vaccines, cancer treatments, and genetic therapies (Haque, 2020; Heine *et al*., 2021). Continuous research focuses on improving carriers and minimizing immune reactions (Corbett, 2020; Maruggi, 2019).

Cumulative toxicity

The use of mRNA treatments, like vaccines and gene therapy, raises concerns about Lipid Nanoparticles (LNPs) accumulating in the liver and spleen, which are crucial for detoxification and immune function (Fang, 2022; Hu, 2020; Janas, 2018; Lv, 2006; Monnery, 2017). LNP accumulation can lead to lasting toxicity. To mitigate this, researchers are creating biodegradable carriers that decompose into safe by products, enhancing safety and delivery (Fischer, 2003; Moghimi, 2005; Kedmi, 2010; Soenen, 2009).

siRNAs can also induce immune responses and toxicity, complicating their clinical use (Dokka, 2000). Pattern Recognition Receptors (PRRs), such as Toll-like Receptors (TLRs), trigger cytokine release, inflammation, and reduced effectiveness (Dokka, 2000). Unmodified siRNAs can cause unintended effects, stress, and cell death, and certain delivery methods may heighten immune activation (Toh, 2009; Horie, 2013).

Potential integration risks

mRNA plays a crucial role in protein synthesis and does not change the host genome, making it suitable for vaccines and treatments (Wolff, 1990). Its stability and translation are influenced by the sequence, cell type, and surrounding environment (Boczkowski, 1996). Since 1990, the use of exogenous mRNA has led to significant advancements in therapeutic and preventive molecular medicine (Hoerr, 2000).

RNA technologies currently facilitate cancer immunotherapy, protein replacement, genome editing, and vaccine development (Hu, 2020). mRNA is responsible for encoding proteins that can fix mutations or enhance immune responses, while siRNA is used to silence detrimental genes associated with diseases (Chavda, 2021). To increase safety, current designs incorporate degradation signals to manage the lifespan of mRNA (Sahin, 2014), striking a balance between effectiveness and risk (Kreiter, 2016). Ongoing studies are focused on improving the performance of mRNA therapies (Zheng, 2000; Vader, 2016).

Emerging strategies to optimize mRNA therapeutics

Advanced delivery systems

Exosomes are natural vesicles that carry biomolecules such as mRNA, providing biocompatibility and targeted gene delivery for cancer with little effect on healthy cells, as depicted in Figure 4 (Sedic, 2018). Dendritic polymers, also known as dendrimers, are branched nanocarriers that can deliver small molecules, proteins, and nucleic acids with great accuracy and absorption. Merging these two systems could improve the effectiveness and safety of therapies, especially in cancer treatment (Li, 2014; Funabiki, 2014).

Bioconjugation technologies

Attaching specific molecules to mRNA delivery systems enhances accuracy by focusing on particular tissues and minimizing systemic side effects. Lipid Nanoparticles (LNPs), which are frequently utilized for mRNA delivery, can be altered with ligands such as galactose to specifically target liver cells through receptor recognition. This approach is particularly beneficial for addressing rare liver-related metabolic disorders by delivering mRNA that encodes functional proteins directly to hepatocytes, thereby restoring function and alleviating symptoms along with off-target effects (Ramírez-Cortés and Ménová, 2025).

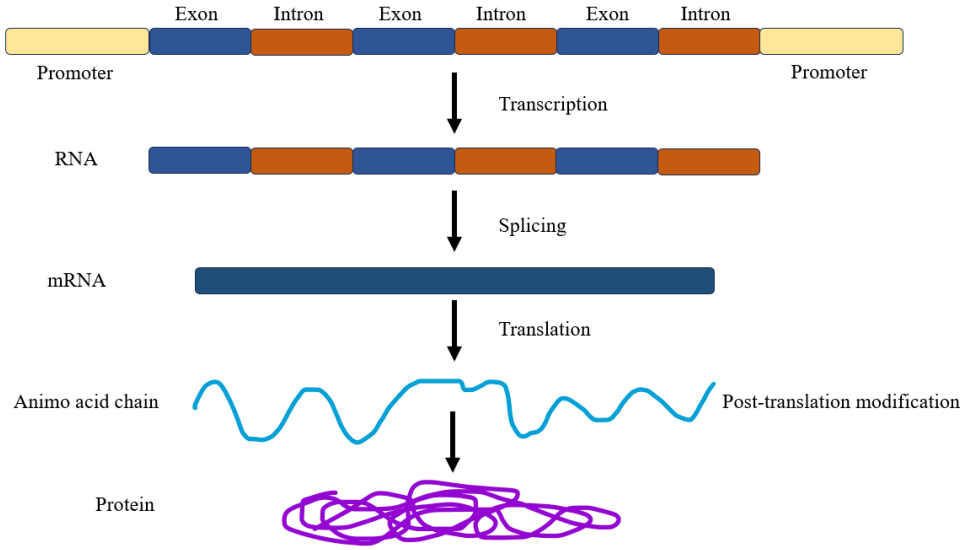


Figure 1: Messenger RNA (mRNA) (Chavda, 2021).

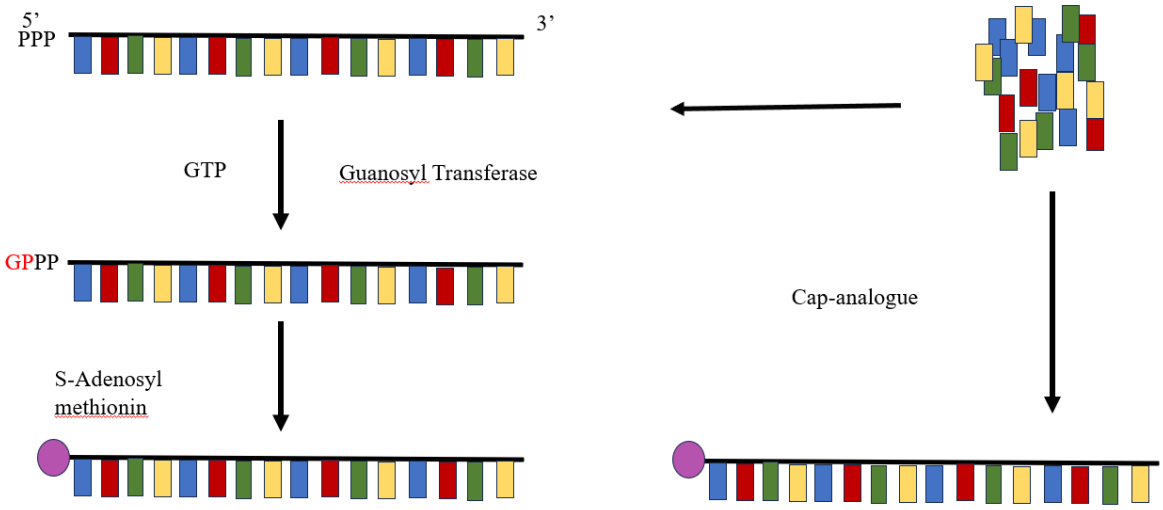


Figure 2: Post-transcriptional capping (left) is a two-step enzymatic process, whereas co-transcriptional capping (right) adds a cap analog during transcription using an enzyme from *in vitro* transcription (Hu, 2020).

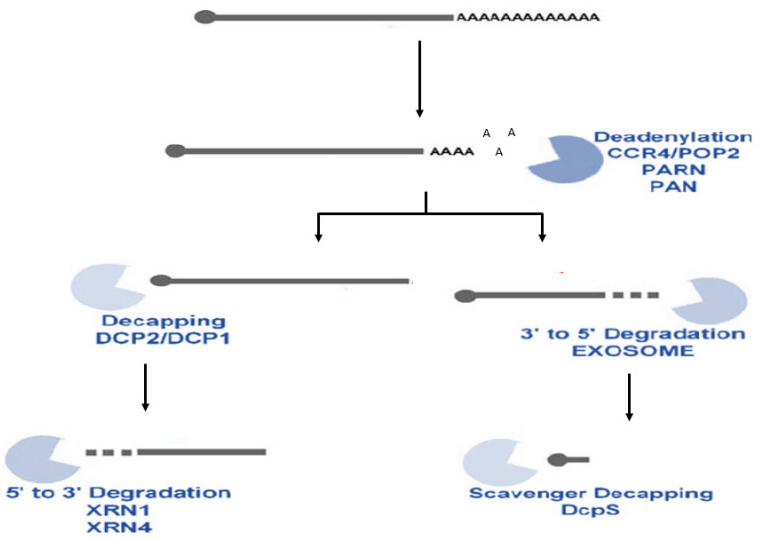
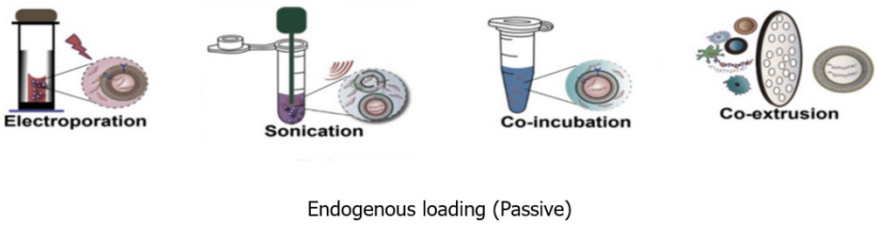


Figure 3: Eukaryotes degrade mRNA to regulate gene expression and control protein production in response to changing conditions (Fischer, 2003).



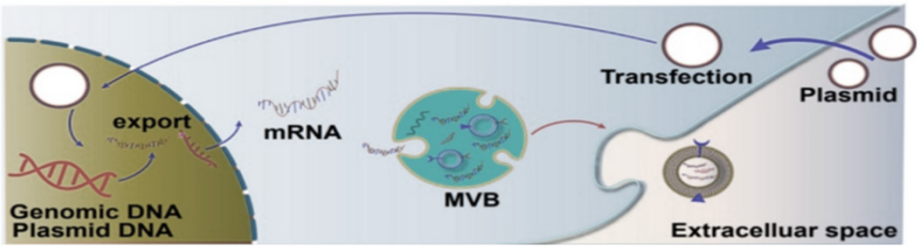


Figure 4: There are various methods for packing cargo into exosomes (Van Hoecke and Roose, 2019).

Crispr-driven optimization

Attaching specific molecules to mRNA delivery systems enhances the accuracy and effectiveness of mRNA therapeutics by allowing targeted delivery to specific tissues, which helps to minimize side effects from systemic distribution. Lipid Nanoparticles (LNPs) are a prominent delivery method, encapsulating mRNA and facilitating cellular entry. When modified with targeting ligands such as galactose-recognized by liver cell receptors-LNPs improve liver-specific delivery. This is particularly beneficial for treating liver-related metabolic disorders resulting from genetic mutations. The targeted delivery of mRNA that encodes functional proteins can restore liver function, alleviate symptoms, and reduce necessary dosages, thereby minimizing off-target effects (Ramírez-Cortés and Ménová, 2025).

CONCLUSION

mRNA therapies mark a significant breakthrough in the treatment of infectious diseases and genetic disorders. Their effectiveness depends on a solid grasp of pharmacokinetics, processing, and possible toxicity. Progress in chemical modifications, delivery methods, and translation efficiency has enhanced stability, minimized immune responses, and allowed for targeted actions. Their applications include vaccines, cancer therapies, and rare genetic disorders, although concerns regarding long-term safety and immune activation remain and immune activation. Emerging tools such as exosome-based delivery and CRISPR systems further expand therapeutic potential. Ongoing collaboration

across disciplines is crucial to ensure a balance between safety and effectiveness in future mRNA therapies.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to the faculty members and management of Vishwakarma University, School of Pharmacy, Pune, Maharashtra, India for providing all necessary technical supports and motivating us throughout the project.

ABBREVIATIONS

mRNA: Messenger RNA; **UTRs:** Untranslated Regions; **LNPs:** Lipid Nanoparticles; **TLRs:** Toll-Like Receptors; **RIG-I:** Retinoic Acid-Inducible Gene I; **DCP1/DCP2:** Decapping Enzymes; **CRISPR**: Clustered Regularly Interspaced Short Palindromic Repeats; **COPD:** Chronic Obstructive Pulmonary Disease; **CFTR:** Cystic Fibrosis Transmembrane Conductance Regulator; **CleanCap:** Co-Transcriptional Capping Enzyme; **HPLC**: High-Performance Liquid Chromatography; **TLR3, TLR7, TLR8:** Toll-Like Receptors 3, 7, and 8; **RSC:** Royal Society of Chemistry; **RNA:** Ribonucleic Acid; **DNA:** Deoxyribonucleic Acid; **5'-cap:** 5-Prime Cap; **N1-methylpseudouridine:** Chemically Modified Nucleoside Used for stability.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Shinde Y, Sharma TP, Shaha A, Chaudhari R, Rajeghorpade R. Metabolism of mRNA Therapeutics: Insights into Pharmacokinetics and Toxicology. Int. J. Pharm. Investigation. 2026;16(2):517-22.