

# Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

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## ABSTRACT

Aging is characterized by progressive molecular and cellular dysfunction, including chronic low-grade inflammation, oxidative stress, endothelial impairment, and reduced regenerative capacity [1-3]. These interrelated processes have stimulated growing interest in genetic therapeutics, particularly microRNAs (miRNAs), because they can modulate multiple pathogenic pathways simultaneously [4-12]. However, nucleic-acid-based anti-aging interventions remain constrained by poor physicochemical stability, rapid nuclease degradation, insufficient cellular uptake, and inefficient intracellular release [13-21]. Drug delivery systems are therefore essential for translating genetic anti-aging strategies into practical therapeutics. Among non-viral platforms, liposomes remain highly attractive because of their biocompatibility, compositional flexibility, cargo-protective capacity, and pharmaceutical scalability [13-21]. This focused review discusses the role of liposome-based systems in the delivery of genetic materials for anti-aging applications, with particular emphasis on miRNA-mediated modulation of inflammaging (i.e., chronic low-grade age-associated inflammation), endothelial dysfunction, and regenerative decline [1-12]. Special attention is given to miR-146a, miR-21, and miR-126 because of their relevance to NF- $\kappa$ B signaling, PI3K/AKT-mediated survival, and vascular homeostasis [7-12,25-31]. The review also compares liposomes with other nucleic-acid carriers, including lipid nanoparticles, polymeric systems, and extracellular vesicles, and highlights translational issues such as formulation stability, endosomal escape, tissue targeting, and safety [13-24]. Overall, liposome-based carriers represent a practical and promising platform for advancing precision anti-aging therapeutics in regenerative medicine.

**Keywords:** Anti-aging therapy; inflammaging; microRNA delivery; liposome; nucleic acid therapeutics; nanocarrier; regenerative medicine; endothelial dysfunction.

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## 1. Introduction

Aging is now recognized as a biologically regulated process driven by interacting hallmarks that include

genomic instability, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion, and altered intercellular communication [1,2]. Among these, chronic sterile

## Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

inflammation has emerged as a central driver of age-associated tissue decline. The concept of inflammaging links persistent inflammatory tone with oxidative stress, endothelial dysfunction, tissue remodeling, and impaired regeneration across multiple organ systems [2,3].

This framework has strengthened interest in molecular interventions that act upstream of overt tissue degeneration. In this context, miRNAs are attractive anti-aging candidates because they regulate gene expression post-transcriptionally and can simultaneously affect multiple biological pathways [4-12]. miRNAs relevant to inflammatory control, endothelial protection, angiogenesis, and tissue repair are especially important in aging-related pathology [7-12,25-31]. However, naked nucleic acids are intrinsically unstable, rapidly degraded in biological fluids, poorly internalized by cells, and often inefficiently released into the cytoplasm after uptake [13-21]. Accordingly, carrier design is a decisive issue in the development of genetic anti-aging therapeutics.

Liposomes remain among the most practical non-viral delivery systems for nucleic acids. Their phospholipid bilayer structure enables cargo protection, compositional tuning, surface modification, and scalable pharmaceutical development [13-21]. This review therefore examines liposome-based delivery of genetic materials for anti-aging therapy, with emphasis on miRNA-oriented strategies targeting inflammaging, endothelial dysfunction, and regenerative decline. Particular focus is placed on miR-146a, miR-21, and miR-126, which together provide a biologically coherent anti-inflammatory, pro-survival, and pro-angiogenic framework [7-12,25-31]. The overall conceptual framework linking aging biology, microRNA cargo selection, liposomal formulation, delivery sequence, and potential translational applications is summarized in Figure 1.

**Figure 1.** Conceptual framework of liposome-mediated microRNA delivery for anti-aging therapy. Aging-associated inflammatory and vascular dysregulation provides the biologic rationale for selecting miR-146a, miR-21, and miR-126 as candidate cargos. Liposomal carrier engineering supports stabilization, cellular uptake, and intracellular release, ultimately linking nucleic-acid delivery to anti-inflammatory, endothelial, and regenerative applications.

### 2. Genetic Materials as Emerging Therapeutics for Anti-Aging Intervention

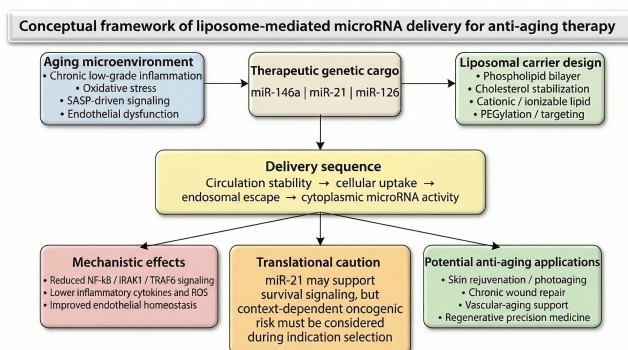
Genetic materials are increasingly investigated as therapeutic tools because they can modulate disease-relevant pathways more precisely than many conventional small molecules [4-6,13-21]. This feature is especially valuable in aging biology, where chronic degeneration arises from network-level dysregulation involving inflammatory mediators, apoptosis regulators, oxidative stress pathways, endothelial signaling, extracellular matrix remodeling, and the senescence-associated secretory phenotype (SASP) [1-3].

Among nucleic-acid platforms, miRNAs are especially relevant because a single miRNA can coordinate multiple targets within one biological circuit [4-12]. This multitarget behavior aligns well with aging, which is driven by interconnected rather than isolated molecular defects. Other genetic modalities, including siRNA, mRNA, antisense oligonucleotides, plasmid DNA, circular RNAs (circRNAs), and other emerging RNA constructs, also hold translational promise, but all remain highly dependent on delivery-system engineering for biological efficacy [13-21]. The principal classes of genetic cargo relevant to anti-aging intervention and their translational characteristics are summarized in Table 1.

### 3. Biological Basis for miRNA-Based Anti-Aging Therapy

The rationale for miRNA-based anti-aging therapy stems from the observation that aging reflects both accumulated damage and dysregulated gene-expression programs [1,2,4-6]. miRNAs can function as systems-level regulators of inflammation, oxidative stress, angiogenesis, senescence, and tissue repair [4-12].

miR-146a is one of the most compelling anti-inflammatory miRNAs in aging-related biology. It suppresses IRAK1/TRAF6 signaling and reduces NF-κB activation, thereby attenuating chronic inflammatory responses [7,11,12]. Experimental data in aged dermal fibroblasts further indicate that miR-146a reduces inflammatory mediators and reactive oxygen species,



## Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

supporting its relevance to skin aging and regenerative repair [11]. Additional skin-focused work also positions miR-146a as a biologically meaningful node across multiple skin-aging pathways [29].

miR-21 is a pleiotropic miRNA involved in survival signaling, apoptosis regulation, remodeling, and endothelial responses. Experimental vascular and cardiac endothelial studies indicate that miR-21 can suppress PTEN and enhance downstream pro-survival or pro-angiogenic signaling, including PTEN/VEGF-related and PI3K/AKT-associated pathways [25,28]. However, miR-21 is also one of the best-established oncomiRs in the broader literature, with repeated links to tumor-promoting phenotypes across multiple cancer types [31]. Accordingly, any anti-aging application of miR-21 should be framed as a tightly controlled, context-dependent strategy that prioritizes local delivery, exposure limitation, and careful long-term oncologic safety assessment rather than indiscriminate systemic upregulation.

miR-126 is a canonical endothelial miRNA that supports vascular integrity, angiogenesis, endothelial repair, and anti-inflammatory endothelial function [7-10,26,27,30]. Because vascular decline is a core component of biological aging, miR-126 is particularly attractive for precision anti-aging interventions seeking to preserve perfusion, endothelial homeostasis, and regenerative responsiveness. Clinical and *ex vivo* aging-related data further support its biomarker and therapeutic relevance [30].

Taken together, miR-146a, miR-21, and miR-126 form a rational triad for anti-aging therapy: suppression of chronic inflammatory signaling, enhancement of cellular survival programs, and support of vascular-endothelial homeostasis [7-12,25-31].

### 4. Why Delivery Systems Are Critical for Genetic Anti-Aging Therapeutics

Despite their biological appeal, nucleic acids are pharmacologically fragile. Naked RNAs are rapidly degraded by nucleases, show poor serum stability, and do not readily cross cell membranes because of their size, hydrophilicity, and negative charge [13-21]. Even after internalization, many remain trapped in endosomes, which substantially reduces effective cytoplasmic delivery [14,17-21].

These barriers are especially problematic in anti-aging therapy, where chronic tissue dysfunction may require repeated dosing and sustained pathway modulation rather than a brief pharmacologic effect [1-3]. An ideal delivery

system should therefore provide cargo protection, favorable particle size, sufficient colloidal stability, safe biodistribution, efficient cellular uptake, endosomal escape, and pharmaceutical manufacturability [13-24].

### 5. Liposomes as a Practical Platform for Anti-Aging Genetic Delivery

Liposomes are phospholipid vesicles capable of encapsulating or complexing hydrophilic genetic cargos while shielding them from degradation [13,15-21]. They are especially attractive for anti-aging applications because they combine biocompatibility, structural versatility, and practical formulation control.

Their lipid composition can be tailored to modulate membrane rigidity, surface charge, fusion behavior, and release characteristics [15-21]. Phosphatidylcholine provides bilayer structure, cholesterol improves membrane stability, and cationic or ionizable lipids facilitate electrostatic interaction with nucleic acids [14-21]. In addition, liposomes can be PEGylated or ligand-modified to improve colloidal stability, prolong circulation, and potentially enhance tissue selectivity [19-21].

Importantly, liposomes also provide the vesicular basis for classical lipoplexes formed after complexation of cationic liposomes with nucleic acids, whereas lipid nanoparticles (LNPs) represent a more specialized extension of lipid-based delivery engineering. While LNPs have achieved substantial clinical success, liposomes remain highly valuable where formulation simplicity, adaptable composition, and scalable development are prioritized [13-21].

### 6. Design Considerations for Liposomal miRNA Delivery

Successful liposomal miRNA delivery depends on rational formulation design. Lipid composition is a foundational determinant of encapsulation, membrane stability, and intracellular delivery [14-21]. Cholesterol content must be optimized because it strongly affects vesicle permeability and stability [20]. Cationic or ionizable lipids improve miRNA complexation and endosomal release, but excessive positive charge may increase cytotoxicity and nonspecific interactions [14,17,18,21].

Particle size and polydispersity influence uptake, dispersion behavior, and tissue access. Nanometric, reasonably monodisperse systems are generally preferred for intracellular delivery [13-21]. Surface charge must also be balanced carefully: strongly cationic systems may enhance interaction with cell membranes but compromise

## Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

tolerability, whereas less cationic or anionic systems may improve biocompatibility at the expense of transfection strength [21].

A further key issue is endosomal escape. Internalization alone is insufficient unless the miRNA can access cytoplasmic silencing machinery. Recent structure-function analyses of cationic and ionizable lipids underscore the importance of lipid architecture in enabling endosomal destabilization and intracellular release [14,17-19].

### 7. Liposomes versus Other Carrier Systems

Alternative platforms for nucleic-acid delivery include viral vectors, polymeric nanoparticles, LNPs, and extracellular vesicles. Viral vectors offer strong transfection efficiency but bring immunogenicity, regulatory, and insertional concerns. Polymeric nanoparticles provide tunable chemistry but may face challenges in biodegradation, toxicity, or batch reproducibility. LNPs are currently the most advanced RNA-delivery systems, but they often depend on sophisticated ionizable lipid chemistry and tightly optimized manufacturing workflows [13-19]. A concise comparison of these carrier platforms is provided in Table 2.

Extracellular vesicles and exosomes are especially attractive in regenerative medicine because of their biomimetic character and inherent biological signaling potential. However, they also pose important translational challenges, including source dependence, heterogeneous cargo composition, difficult purification, and batch variability [22-24]. Recent comparative analyses indicate that, from a pharmaceutical development standpoint, lipid-based synthetic systems remain easier to standardize, characterize, and scale [22]. For anti-aging indications that may require repeated administration and long-term quality consistency, this is a substantial advantage.

### 8. Relevance to Skin Aging, Vascular Aging, and Regenerative Medicine

The anti-aging field is particularly suitable for miRNA-based delivery because aging involves convergent inflammatory, vascular, and reparative failure rather than single-gene pathology [1-12]. This is highly relevant in dermatology and regenerative medicine, where skin aging, impaired wound healing, endothelial decline, and chronic inflammatory remodeling intersect biologically [10-12,23-30].

Liposome-mediated delivery of miR-146a, miR-21, and miR-126 therefore provides a coherent translational concept. miR-146a addresses inflammatory and oxidative

components of tissue aging [11,29]; miR-21 relates to survival and stress-response signaling but also requires explicit consideration of dose, tissue selectivity, and oncogenic risk [25,28,31]; and miR-126 supports endothelial repair and angiogenic competence [7-10,26,27,30]. Beyond skin rejuvenation, this framework may also be relevant to chronic wounds, diabetic vascular impairment, ischemic repair, and broader regenerative longevity strategies.

### 9. Conclusion

Liposome-based carriers occupy a strong translational position in the development of genetic anti-aging therapeutics. Their value lies not only in cargo protection and delivery efficiency, but also in their pharmaceutical adaptability, compositional control, and scalability relative to many biologically derived vesicle systems [13-24]. In anti-aging applications, this is particularly important because durable benefit depends on sustained modulation of inflammatory, endothelial, and regenerative pathways rather than brief symptomatic effects [1-12].

Among candidate cargos, miR-146a, miR-21, and miR-126 are especially attractive because they collectively address core features of age-related dysfunction, including chronic inflammation, impaired cellular resilience, and vascular decline [7-12,25-31]. For miR-21 in particular, translational development must explicitly address oncogenic risk, dose limitation, and tissue selectivity [31]. Although further work is needed to optimize targeting, intracellular release, safety, and biological validation, current evidence supports liposomal delivery as one of the most practical platforms for advancing nucleic-acid-based anti-aging intervention toward regenerative and precision medicine.

**Table 1. Genetic materials relevant to anti-aging therapy**

Genetic material	Main mechanism	Potential anti-aging relevance	Main delivery challenge	Suitability for liposomes
miRNA	Post-transcriptional multi-target regulation	Inflammation, endothelial dysfunction, angiogenesis	Instability, off-target biodistribution, endosomal trapping	High

## Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

Genetic material	Main mechanism	Potential anti-aging relevance	Main delivery challenge	Suitability for liposomes
		Regeneration, regeneration		
siRNA	Sequence-specific mRNA silencing	Targeted inhibition of pro-senescence mediator	Serum instability, intracellular release	High
mRNA	Transient therapeutic protein expression	Regenerative or cytoprotective protein replacement	Large cargo, immunogenicity, formulation complexity	Moderate to high
Antisense oligonucleotide	RNA binding and translational inhibition or splice modulation	Selected anti-aging targets	Repeated dosing, tissue penetration	Moderate
Plasmid DNA	Transgene expression	Long-term regenerative strategies	Nuclear entry barrier, low transfection efficiency	Moderate
circRNA/advanced RNAs	Stable regulatory or coding	Emerging longevity and	Early-stage development	Exploratory

Genetic material	Main mechanism	Potential anti-aging relevance	Main delivery challenge	Suitability for liposomes
	RNA constructs	regenerative applications		

**Table 2. Comparison of carrier systems for genetic anti-aging delivery**

Carrier system	Strengths	Weaknesses	Translational practicality
Viral vectors	High transfection efficiency	Immunogenicity, regulatory burden, insertional concerns	Moderate
Polymeric nanoparticles	Tunable chemistry, controlled release	Potential toxicity, complex optimization	Moderate
LNPs	Strong RNA-delivery efficiency, clinically validated	Advanced chemistry and manufacturing requirements	High
Extracellular vesicles/exosomes	Biomimicry, regenerative signaling	Heterogeneity, source dependence, scale-up difficulty	Moderate
Liposomes	Biocompatible, versatile, scalable, compositionally defined	Need optimization for targeting and endosomal escape	High

# Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

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## Liposome-Based Delivery of Genetic Materials for Anti-Aging Therapy: A Focused Review of microRNA-Oriented Translational Strategies

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