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Endogenous Mechanisms for Nanoparticle-Based Nucleic Acid Delivery

Introduction

Achieving targeted delivery of nucleic acids to specific tissues and cells presents a challenging obstacle in biomedical research and therapeutic development. Overcoming these barriers necessitates innovative strategies, with different types of nanoparticle formulations emerging as promising solutions. When engineered specifically, nanoparticles offer a versatile platform for improving the precise delivery of nucleic acid using endogenous mechanisms for a targeted approach.

This article will provide an overview of the multifaceted approaches to overcome delivery challenges, including the examination of nanoparticle formulations with a specialized emphasis on extrahepatic delivery. Central to the discourse are three distinct strategies:

The Role of Protein Corona on Tissue and Cell-Specific Targeting

The interaction between nanoparticles and proteins in biological fluids, forming a surface protein corona, can influence the targeting ability of nanoparticles to specific tissues and cells. Understanding and manipulating this protein corona can enhance the specificity and efficiency of nucleic acid delivery.

Peritoneal Macrophage Tropism to Disease Sites

Leveraging the natural tropism of peritoneal macrophages to disease sites presents a promising approach for targeted nucleic acid delivery. By utilizing nanoparticle formulations designed to exploit this tropism, researchers can enhance the accumulation of nucleic acids at disease sites, improving therapeutic outcomes.

Extracellular Vesicle-Mediated In Vivo Delivery

Extracellular vesicles play a crucial role in intercellular communication and can serve as natural carriers for nucleic acids. Understanding how to harness and engineer extracellular vesicles for targeted delivery holds great potential for enhancing the efficacy and specificity of nucleic acid therapeutics.

Peritoneal Macrophage Tropism to Disease Sites

The five-year survival rate for pancreatic cancer is notably poor, underscoring the urgency for improved therapeutic strategies. Pancreatic tumors present a complex and diverse cellular composition, encompassing not only malignant cells but also a variety of other cell types, among which tumor-associated macrophages (TAMs) play a significant role. Pancreatic cancer exhibits a pronounced abundance of these TAMs.

The approach of peritoneal macrophage tropism to disease sites is to investigate the feasibility of reprogramming the peritoneal macrophages, enabling them to uptake nanoparticles and navigate toward areas of injury or disease via selective tropism. Once in the pancreatic tumor, these macrophages can alter the immune compartment of the tumor leading to enhanced antitumor efficacy. To address this, researchers utilized macrophages residing in the peritoneal cavity. These mature macrophages serve as ideal candidates for nanoparticle delivery vehicles. By injecting nanoparticle-based delivery systems into the peritoneal cavity to target macrophages, a switch in phenotype is induced, subsequently influencing the tumor microenvironment toward an anti-tumor role.

MicroRNAs (miRNAs) represent a class of non-coding RNA molecules that play crucial roles in regulating various cellular functions. Within the intricate landscape of the immune system, macrophages serve as key orchestrators of immune responses, capable of adopting diverse phenotypes in response to microenvironmental cues.

Of notable interest is the ability of specific miRNAs to reprogram macrophages, steering them toward an anti-tumor phenotype. This phenomenon holds immense therapeutic potential, as it allows for the manipulation of macrophages to combat tumor growth and progression. By targeting and altering the expression of select miRNAs, researchers can shift macrophage behavior, promoting their anti-tumor activity.

This approach showcases the potential of utilizing peritoneal cavity injection and macrophages as a “Trojan horse” for targeted pancreatic cancer therapy. By delivering miRNA-modulating agents directly into the peritoneal cavity, where macrophages reside, researchers can effectively harness the innate migratory capacity of these immune cells. Once internalized by macrophages, the therapeutic agents can exert their effects, reprogramming the macrophages to adopt an anti-tumor phenotype.

This strategic approach capitalizes on macrophages’ inherent migratory behavior towards areas of injury or disease, guided by selective tropism. By leveraging these endogenous mechanisms, the aim is to target pancreatic tumors more precisely. The therapeutic agent employed in this paradigm is nucleic acid molecules, which hold promise for targeted and effective treatment strategies against pancreatic cancer.

Extracellular Vesicle-Mediated *In Vivo* Delivery

There is promising research on the potential of extracellular vesicles (EVs) to facilitate therapeutic delivery within the body, particularly in the context of cancer. EVs, secreted from cells, serve as effective mediators of intercellular communication, akin to brief messages exchanged between donor and recipient cells. With various payloads, including microRNAs and mRNAs, EVs present an intriguing avenue for therapeutic intervention, especially in ovarian cancer. The focus lies in understanding the mechanisms of underlying disease relapse following treatment, particularly in cases where ovarian cancer becomes resistant to chemotherapy over time.

To investigate this, researchers developed a resistant relapse model of ovarian cancer in mice. Through a rigorous regimen involving chemotherapy followed by cessation to allow tumor regrowth, the researchers observed a recurrence of tumors in treated animals, indicative of chemotherapy resistance. Subsequent genetic analysis of the tumors revealed that tumors treated with chemo-drug paclitaxel had significantly lower expression of a particular microRNA, miR-Let7b, associated with tumor suppression.

Researchers then focused on harnessing the efficacy of miR-Let7b in suppressing tumor growth. Notably, the combination of miR-Let7b with other therapeutic agents yielded pronounced effects, suppressing tumor growth and a notable reduction in biomarkers associated with cancer progression. Moreover, the researchers observed that the EVs secreted by the cancer cells contained high levels of miR-Let7b in the peritoneal fluid, suggesting a potential mechanism for propagating therapeutic effects beyond the site of administration.

The concept of the bystander effect, analogous to navigating a bustling city with limited access, underscores the potential of EVs to disseminate therapeutic payloads to distant sites within the body. By harnessing EVs as molecular “bicycles,” researchers aim to augment the efficacy of traditional nanoparticle-based delivery systems, enhancing therapeutic outcomes.

These findings present a promising avenue for future research, offering insights into novel strategies for targeted therapeutic delivery and overcoming the challenges associated with cancer treatment relapse.

Conclusion

In conclusion, the exploration of endogenous mechanisms for nanoparticle-based nucleic acid delivery represents a significant advancement in biomedical research and therapeutic development. By examining diverse nanoparticle formulations, this article has shed light on innovative strategies to overcome delivery challenges and enhance targeted nucleic acid delivery to specific tissues and cells.

The utilization of the protein corona approach has demonstrated the potential to tailor lipid nanoparticles for precise tissue and cell-specific targeting, thereby improving delivery efficiency and therapeutic efficacy. By modifying the surface chemistries of lipid nanoparticles, researchers can selectively enrich specific proteins from blood or plasma, enhancing their ability to navigate to intended target sites beyond the liver.

Furthermore, the investigation into peritoneal macrophage tropism to disease sites has revealed promising avenues for targeted therapy, particularly in pancreatic cancer. By leveraging macrophages as a “Trojan horse” for nanoparticle delivery, researchers aim to effectively reprogram these cells to target tumor microenvironments. This approach capitalizes on macrophages’ inherent migratory behavior towards areas of injury or disease, offering an advantageous strategy for precise and effective therapeutic delivery.

Additionally, the exploration of extracellular vesicle-mediated in vivo delivery has highlighted the potential of these vesicles to facilitate intercellular communication and propagate therapeutic effects beyond the site of administration. By harnessing extracellular vesicles as molecular carriers, researchers aim to increase the efficacy of traditional nanoparticle-based delivery systems, offering novel insights into targeted therapeutic delivery strategies.

Overall, the findings presented in this article underscore the importance of leveraging endogenous mechanisms for nanoparticle-based nucleic acid delivery to advance therapeutic interventions in various disease contexts. By expanding our understanding of these mechanisms, researchers can develop more effective and clinically translatable delivery vehicles, ultimately improving patient outcomes and advancing precision medicine.

Ascendia’s expertise in tailored approaches for encapsulating large molecules and biologics in LNPs could pave the way for the development of innovative medicines for life-threatening diseases.