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A Novel Integrated Therapeutic Strategy for Pancreatic Ductal Adenocarcinoma Based on Synergistic siRNA and Intelligent Nanocarriers

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Abstract. Pancreatic Ductal Adenocarcinoma (PDAC) stands among the most aggressive forms of cancer. Its clinical treatment confronts two core difficulties. On one hand, over 90% of cases carry KRAS gene mutations. Yet the mutant KRAS protein lacks traditional binding pockets for drugs. This has long made it an undruggable target. On the other hand, PDAC tumors are wrapped in a dense, fibrotic stroma. This stroma acts as a tough barrier. It greatly limits how well therapies can enter and accumulate inside the tumor. Conventional treatments often fail against both challenges. Thus, their efficacy remains limited. The work builds on the pathological mechanisms of PDAC. Here, oncogenic KRAS signaling drives two processes: tumor cell growth and stromal remodeling. We propose a new integrated and synergistic treatment paradigm. This strategy brings together two core modules. First is a synergistic silencing module. It uses combinatorial siRNA to silence KRAS and key downstream signaling nodes at the mRNA level. This aims to overcome single-target limits and signaling compensation that causes resistance. Second is an intelligent delivery platform. It involves a multifunctional, biodegradable nanocarrier. This carrier integrates surface engineering, active targeting, stimulus-responsive release, and endosomal escape. In this way, it systematically overcomes biological barriers from circulation to cytoplasmic release. This allows precise, efficient siRNA delivery. This strategy's innovation lies in a shift in paradigm. It moves from passive, single-target delivery to intelligent, synergistic delivery against multiple targets. It targets tumor cells and their supportive microenvironment together. Therefore, it provides a systemic solution. It holds clear potential for clinical translation in overcoming PDAC treatment resistance.

Keywords: pancreatic ductal adenocarcinoma, KRAS, small interfering RNA, nanocarrier, synergistic therapy

1. Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) carries an extremely poor prognosis. Its hallmark pathological features include highly heterogeneous tumor cells and a dense, fibrotic stromal sheath-termed desmoplasia. Together, these create an immunosuppressive cold tumor phenotype. They also confer strong therapy resistance [1]. More than 90% of PDAC cases show gain-of-function

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mutations in the KRAS gene. Persistent activation of this driver gene is central to PDAC initiation and maintenance [2].

Current standard treatment for PDAC still relies mainly on surgery and systemic chemotherapy. Regimens include gemcitabine or FOLFIRINOX. However, efficacy remains limited. These approaches offer only minimal improvement in patient survival [3]. This therapeutic bottleneck comes from two connected obstacles. First, at the target level, the mutant KRAS protein is notoriously hard to inhibit directly. Traditional medicinal chemistry struggles because its surface lacks deep, hydrophobic pockets for high-affinity small-molecule binding. Thus, it has been labeled undruggable [4]. Second, at the delivery level, PDAC tumors contain an exceptionally abundant extracellular matrix and activated cancer-associated fibroblasts. These form a dense physical barrier. This greatly hinders drug diffusion and enrichment within the tumor parenchyma [5].

RNA interference (RNAi) technology offers a different path. In particular, exogenous small interfering RNA (siRNA) gives a novel theoretical route to target undruggable KRAS [6]. siRNA works through a highly sequence-specific mechanism. The double-stranded siRNA is recognized and processed by the cellular Dicer enzyme. Then it is incorporated into the RNA-induced silencing complex (RISC). Inside RISC, the Argonaute 2 (Ago2) protein uses the siRNA antisense strand as a guide. It identifies and interacts with the target mRNA through the base-pair complementarity. This promotes the cleavage of mRNA [7,8]. The outcome is the degradation of the target mRNA. The corresponding protein synthesis is inhibited on the translational level. The mechanism in this regard does not rely on the 3D structure of the protein. Hence, it will be able to overcome the natural complexity of targeting KRAS protein directly. It represses oncogenic activity of the root [2,4]. Nevertheless, siRNA per se has problems in terms of delivery. It is a highly negative macromolecule that is hydrophilic. Passive diffusion across the cell membrane that are similarly charged is prevented by repulsive electrostatic forces. It is prone to quick nuclease degradation in systemic circulation. It also has a high rate of renal clearance. In addition, the majority of siRNA that gains access to the cell via endocytosis is entrapped at the endolysosome pathway. There it is degraded. It does not attack the cytoplasmic site of action [9,10]. As a result, it is important to create effective systems of delivery. To achieve the therapeutic potential of siRNA, they have to do away with these physiological barriers.

According to the further evidence of the KRAS signaling dual role in PDAC and stimulation of tumor cell proliferation and pro-fibrotic microenvironment at the same time, the article suggests a new synergistic therapeutic approach [11]. The main concept is to create a unified platform. This system integrates synergistic, combo siRNA-based targeting of the KRAS network and a multifunctional nanocarrier. The carrier will be smart to undergo various in vivo barriers. In this way, the approach will present a novel systemic approach to cancer treatment. It particularly applies in the case of refractory solid tumors of PDAC. Its value is shown in two ways. It targets the invasive undruggable core oncogene KRAS using siRNA. It also intelligently frees the stroma barriers of drug delivery with a dense stroma by an intelligent nanocarrier. Finally, by acting on tumor cell-autonomous signals and supportive microenvironment concomitantly, the approach of this strategy is to be grounding breaking. It shifts the mode of attack that is single-point to single-point disruption. This presents a novel avenue having considerable translational opportunities. It has the potential to enhance the clinical outcome of PDAC.

2. Pathological basis of PDAC

The pathobiology of PDAC is a factor that leads to the dilemma in its treatment. It has been shown, that oncogenic KRAS signaling is a central role in PDAC, going way beyond tumor cell

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proliferation. The pancreatic tissue has been found to have a primordial compartment, Pancreatic Duct Glands (PDGs), that is a regenerative PT with repair characteristics of ductal epithelia in response to injury such as pancreatitis [12]. In the development of PDAC, there is a possibility of oncogenic KRAS signaling disabling this regenerative program. The uncontrolled growth of the PDGs can equally be triggered by the concomitant loss of major protective factors, including TFF2 (Trefoil Factor 2) that follows a series of stages to pancreatic intraepithelial neoplasia and ultimately invasive PDAC [13].

Molecular mechanism Oncogenic mutations in KRAS (e.g., G12D, G12V) result in unstable KRAS protein in the GTP-bound, activated form by blocking intrinsic GTPase activity, and by blocking GTPase-activating protein (GAP) interactions. This directly subsequent activates various downstream effector signaling pathways including the RAF -MEK-ERK (MAPK) pathway and the PI3K-Akt (pathway) pathway as both an overview of central mediators of its oncogenic actions [2,14]. Activation of MAPK cascade by KRAS involves activation of RAF kinases (such as BRAF), thus leading to cell proliferation and cell survival. At the same time, it may directly/indirectly stimulate PI3K which, in turn, controls cell metabolism, growth, and resistance to apoptosis via AKT [2,14]. It is noteworthy that these pathways interact in a complicated crosstalk and feedback control and that often inhibition of one of the pathways becomes ineffective and may cause a compensatory activation [2,11].

More importantly, non-cell autonomous effects of oncogenic KRAS signaling are also substantial. It passively enhances the activation and proliferation of the Cannabis-Associated Fibroblasts (CAFs) within the tumor stroma by upregulating the expression of the cytokine Transforming Growth Factor 2 (TGF 2) thereby initiating the development and remodelling of the thick fibrotic connective tissue matrix [2,11]. The stroma seems to supply growth factors and metabolic functions to cancer cells. Simultaneously, it represents a strong barrier to drug administration both physically and chemically, and promotes an immunosuppressive microenvironment. Thus, KRAS signaling in PDAC simultaneously mediates the malignant phenotype of the tumor cells and the tumor-promoting properties of the stromal microenvironment and supports each other mutually, together maintaining the progression of the disease process and resistance to therapy.

3. Synergistic therapeutic strategy for PDAC

3.1. siRNA-mediated KRAS targeting and its limitations

Striking oncogenic KRAS has historically been the objective in the treatment of PDAC, and or siRNA technology can offer a distinct resolution to this issue since, in contrast to small-molecule inhibitor or monoclonal antibody that should unavoidably bind and alter a folded protein, siRNA will act at the level of the mRNA encoding KRAS [7]. Upon successful endosomal delivery of a functional siRNA duplex, one of the strands of the duplex gets loaded into RISC and the complex interacts with the target KRAS mRNA in a sequence specific fashion and cleaves it through the Ago2 protein [8]. The splintered mRNA is destructively degraded, effectively silencing the generation of mutant KRAS protein on the translational stage. This is the mechanism that enables siRNA to bypass the structural problem of KRAS protein having no optimal drug-binding sites. It targets the crossing point of gene expression, and, in theory; it could be used in an efficient and specific way to avoid the oncogenic role of KRAS [4,6].

Broadly speaking, no matter how beneficial the use of naked siRNA in cells appears to be mechanistically, there is overwhelmingly strong delivery challenges associated with its use in vivo

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which are mainly attributed to its physicochemical characteristics and baffling in vivo metabolism [9]. The combinatorial siRNA synergistic silencing module that was used in this study has several important benefits over siRNA approaches that target a single gene. First, it allows the deeper blockade of the oncogenic signaling pathway by activating the upstream driver KRAS along with its principal downstream effectors (e.g., MEK, PI3K), and placing strain on the pathway at multiple nodes. This essentially decays activation of by-pass or feedback up-regulation stimulated by inhibition of one node. Second, this approach allows overcoming or postponing the development of drug resistance since it is rare that the tumor cells will evade the inhibition of both key nodes by performing adaptive modifications in one gene. Therefore, it improves the sustainability of the therapeutic pressure. Lastly it allows simultaneous action to the tumor cells and the microenvironment. This strategy will concomitantly target the tumor by extending the targets to major factors which mediate stromal remodeling and will deliver more potent antitumor responses. Nevertheless, siRNA by itself is a highly negatively charged and hydrophilic macromolecule. It is electrostatically repelled by the comparatively negatively charged cell membrane, and therefore does not passively diffuse across the membrane. Moreover, unprotected siRNA can be easily digested by nucleases that are common in plasma and tissues resulting in very short systemic exposure. Moreover, a small molecular weight (approximately, 13kDa) and hydrophilicity are the factors that predispose siRNA to hasty renal clearance through glomerular filtration. Most importantly, despite the ability of siRNA to be transported into cells through recycled endocytosis, over 99 percent of the siRNA remains entraped in organelles which are surrounded by membranes such as endosomes and is finally broken down in lysosomes without being deposited within the cytoplasmic RISC to have its actio [9-10]. Thus, it is a precondition to translate siRNA therapy into clinical reality with the help of the carrier systems able to offer siRNA protection, extend its circulation period, stimulate its accumulation in the target cells, and ensure effective delivery into the cytoplasm.

3.2. The integrated synergistic strategy: employing intelligent nanocarriers to solve siRNA delivery

To overcome the target and drug delivery challenges of PDAC all together, this paper suggests the combination therapeutic approach, which intimately combines synergistic silencing with smart delivery. The intelligent delivery systems will have the responsibility of transporting and breaching all biological obstacles between intravenous injection and cytoplasmic location of action so that the friendly and safe delivery of the interaction silencing module can be done. Combinatoric siRNA suppressed the KRAS signaling network into PDAC tumor cells. This is aimed at obtaining root-level inhibition of the main oncogenic pathways.

3.2.1. The synergistic silencing module

In order to combat the redundancy and compensatory potential of the KRAS signaling network, the paper proceeds to use multi-target, synergistic pharmacological approach. The design has the advantage of two levels and it has benefits over the single siRNA approaches. First, on a signaling pathway level, an siRNA cocktail is created that is meant to target KRAS itself and important downstream effector molecules (e.g., MEK, the catalytic subunit p1102a of PI3K) simultaneously. This bis- Nap inhibitory format is sought to provide superior blockage of the oncogenic signal transmission and prevent bypass activation of the pathway or feedback up-regulation in response to the inhibition of one node resulting in their overcoming of drug resistance and more significant antitumor effect [2,11]. Preclinical examination, presents evidence-of-concept. Combination of

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PI3K/mTOR inhibitor NVP -BEZ235 and single-agent MEK inhibitor ARRY -142886 in a mouse lung cancer model modeled by KRAS G12D resulted in greater tumor regression than control of the disease with either inhibitor alone [11]. Second, on the cellular source and the microenvironment level, where PDGs are regarded as the source of precancerous lesions and the malignant transformation of which is associated with the loss of certain factors (e.g., TFF2) [13], the siRNA cocktail may be extended to important nodes that regulate PDGs homeostasis or stromal remodeling. Therefore, it became possible to intervene earlier in the progression of the disease, through either suppressing the action of pro-fibrotic factors by means of siRNA, or, providing protective genes.

3.2.2. The intelligent delivery module

In order to address the in vivo bottlenecks of delivery of siRNA via delivery systems, this paper develops a multifunctional, biodegradable nanocarrier, consisting of modulable functional units to overcome various barriers. A circulation escape system is based on the use of surface polyethylene glycol (PEG) or biomimetic membrane coating to limit opsonin adsorption and recognition by the mononuclear phagocyte system in order to extend the blood circulation half-life. Its conjugated specific ligands, e.g., peptides, or antibody fragments that are targeted at tumor vasculature or overexpressed cell surface receptors, are used by a targeting unit to increase the specific accumulation of the carrier in tumor tissue. This increases the EPR effect and endocytosis of tumor cells. In a responsive release concept, bonds or materials that respond to microenvironmental features of the tumor (e.g. low pH, enzyme particularity) are used so that when the target site is reached the release of the siRNA can be triggered. This accelerates localized concentration as well as decreasing systemic exposure. An endosomal evasion module carries useful materials with a protonsponge effect (e.g. polyethyleneimine analogs) or a membrane-destabilizing effect to help the carrier escape endosomal vesicles into the cytoplasm- an essential requirement of siRNA action [9,15]. In summary, the design of this intelligent nanocarrier aims to systematically address the fThe core difficulties in siRNA delivery outlined earlier. Against nuclease degradation and renal clearance, the circulation escape unit (e.g., PEGylation) provides protection and extends half-life. Against the lack of targeting and tumor enrichment, the targeting unit (e.g., ligand conjugation) enhances active accumulation in tumor tissue. Against endosomal/lysosomal entrapment post-endocytosis, the endosomal escape unit (e.g., proton-sponge materials) facilitates siRNA release into the cytoplasm. To further improve efficacy and safety, the responsive release unit enables triggered drug release at the tumor site. Thus, this carrier system forms a functional closed loop designed to deliver siRNA precisely and efficiently to its cytoplasmic site of action. The intelligent nanocarrier precisely navigates and breaches layer upon layer of barriers. The synergistic siRNA serves as the therapeutic warhead, released within target cells to execute a multi-layered strike on the signaling network. The innovation of this strategy lies in its systemic design thinking. It no longer views the target and delivery problems in isolation but treats them as an integrated whole that must be solved synergistically. By simultaneously intervening in tumor cell autonomous proliferation signals and their supportive microenvironment, this strategy offers a new possibility for overcoming the complex treatment resistance of PDAC. Although this integrated strategy is primarily a preclinical concept, its core technological components have shown promising clinical translation potential in related fields. For instance, the successful approval of oral small-molecule inhibitors targeting the KRAS G12C mutation (e.g., Sotorasib, Adagrasib) validates the clinical feasibility of directly targeting KRAS and also provides encTheagement for RNAi-based deep inhibition strategies. Regarding delivery systems, the successful use of lipid nanoparticle (LNP) carriers for COVID-19 mRNA vaccines, alongside the approval of the first liver-targeted siRNA

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drug Patisiran, fully demonstrates the great potential of nanocarriers for efficient, targeted nucleic acid drug delivery. However, applying such systems to PDAC still faces unique challenges. These include the extreme density of the pancreatic tumor stromal barrier, the need to optimize delivery efficiency to non-hepatic organs, and the long-term management of potential immunogenicity. Future work requires comprehensive validation of this strategy's safety and efficacy in more clinically relevant PDAC animal models (e.g., patient-derived xenograft models, genetically engineered mouse models). Concurrently, optimizing the targeting precision and delivery efficiency of the carrier is crucial to ultimately advance its translation into clinical research raft models, genetically engineered mouse models). Concurrently, optimizing the targeting precision and delivery efficiency of the carrier is crucial to ultimately advance its translation into clinical research.

4. Discussion and outlook

The synergistic strategy proposed in this research aims to directly confront the two core obstacles in PDAC clinical therapy. Compared to traditional chemotherapy and single-targeted therapies, this strategy attempts to achieve a paradigm shift through molecular-level combinatorial gene silencing and delivery-level intelligent engineering. It shifts from a passive attack on a single target towards an active, precise, and synergistic intervention against both the oncogenic signaling network and the supportive microenvironment. This provides a new perspective for improving the current unsatisfactory efficacy of PDAC and demonstrates potential clinical translation value.

Future research can deepen and expand in the following directions. First, regarding target precision, as understanding of the biological characteristics of different KRAS mutant subtypes (e.g., G12D, G12V, G12C) deepens, allele-specific siRNAs can be designed. Combined with genotyping of patient tumors, this could enable truly individualized precision therapy [2]. Second, the nanocarrier platform is highly flexible. It can co-deliver siRNAs or small-molecule drugs targeting other synergistic targets (e.g., immune checkpoint molecules, key metabolic enzymes) to form a cocktail combination therapy that tackles tumor heterogeneity and evolved resistance [2]. Furthermore, for clinical translation, a thorough evaluation of the system's safety and pharmacokinetics is essential. This requires systematic investigation of the biocompatibility of degradable materials, the in vivo distribution and clearance pathways of the carrier, potential immunogenicity, and long-term toxicity. Optimizing the selectivity and affinity of targeting ligands could maximize therapeutic efficacy while minimizing off-target effects on normal tissues. Subsequent work needs rigorous preclinical validation in large animal PDAC models to lay a solid foundation for human clinical trials.

5. Conclusion

The therapeutic dilemma of Pancreatic Ductal Adenocarcinoma demands that we confront its challenges with novel perspectives and integrated strategies. Based on an in-depth analysis of the dual role of KRAS signaling in PDAC, this paper proposes a novel integrated therapeutic strategy combining synergistic gene silencing and intelligent delivery. Conceptually, it breaks through the limitations of traditional single-target thinking by treating the tumor cell's intrinsic oncogenic program and the extrinsic stromal microenvironment as an integrated system requiring coordinated intervention. In design, it innovatively combines combinatorial siRNA therapy targeting the KRAS signaling network with multifunctional nanocarrier technology capable of overcoming multiple in vivo barriers, forming a logically coherent, functionally closed-loop therapeutic scheme.

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This work not only provides a specific RNAi-based technical path for targeting the undruggable KRAS, but more importantly, it demonstrates an expandable platform-based approach. This platform holds promise as a foundation for further integrating other treatment modalities (e.g., chemotherapy, immunotherapy), offering more possibilities for ultimately conquering this intractable malignancy. Although the road ahead remains challenging, such synergistic strategies, which fuse deep molecular biological insights with advanced nano-engineering technology. Undoubtedly represent an important future direction in cancer therapy.

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