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Nanoparticle-siRNA: A potential cancer therapy?

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ABSTRACT

Purpose: To explore current developments in short interfering RNA (siRNA) delivery systems in nanooncology, in particular nanoparticles that encapsulate siRNA for targeted treatment of cancer. siRNA has a high specificity towards the oncogenic mRNA in cancer cells, while application of nanoparticles can improve stable delivery and enhance efficacy.
Methods: A literature search was performed using the terms "siRNA", "nanoparticles", "targeted delivery", and "cancer". These databases included Medline, Embase, Cochrane Review, Pubmed, and Scopus.
Results: siRNA anti-cancer drugs utilize endogenous RNAi mechanisms to silence oncogene expression, which promotes cancer remission. However, current delivery methods have poor efficacy, requiring assistance by nanoparticles for successful delivery. Recently several preclinical studies have crossed into clinical trials utilizing siRNA nanoparticle therapeutics.
Conclusion: Great potential exists for nano-siRNA drugs in cancer treatment, but issues exist with nanoparticle toxicity and off target siRNA effects. Further research is needed in this rapidly developing and promising field of nano-siRNA drugs.

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1. Introduction

1.1. RNA interference

The RNA interference (RNAi) mechanism was first discovered in Caenorhabditis elegans when double-stranded RNA (dsRNA) exogenously introduced caused a transitory depression of gene expression. As silencing mechanism was systemic, it was hypothesized that the RNAi effect was facilitated by a stable intermediate (Sen and Blau, 2006; Dogini et al., 2014). Further investigations led to the discovery of other intermediates such as the dicer enzymes and the RNA-induced silencing complex (RISC) (Sen and Blau, 2006). Interaction between complementary strands of siRNA and messenger RNA (mRNA) forms the basis of RNAi (Resnier et al., 2013). RISC is a complex of proteins and siRNA molecules. The highly conserved Argonaute protein, Argonaute-2 (AGO2) forms the catalytic core of RISC. These two main stages in which gene silencing can occur are: post-transcriptional gene silencing (PTGS), and transcriptional gene silencing (TGS) (Dogini et al., 2014; Castanotto and Rossi, 2009). PTGS can be classified into two general mechanisms, mainly direct sequence-specific cleavage and translational repression and RNA degradation. Perfectly complementary between siRNA and target mRNA will result in sequence-specific cleavage by RISC. Translational repression through RNA degradation is often mediated by miRNAs and can occur despite limited complementarity to target mRNA. Both methods lead to a specific repression effect (Castanotto and Rossi, 2009; Patil et al., 2014). The siRNAs can be transfected into cells, where they bind to RISC and harness the endogenous PTGS mechanism to target and silence specific genes. The siRNA acts as a guide for RISC for recognition of targeted gene sequence (Castanotto and Rossi, 2009; Patil et al., 2014). Before therapeutic application of synthetic siRNA, large-scale siRNA screening is performed to identify potential targets and select for the most potent siRNA for successful gene silencing. Synthetic siRNAs are around 22 nucleotides with 3′ dinucleotide overhangs that mimic dicer cleavage products to facilitate binding to RISC. Synthetic siRNAs seems to hold the most therapeutic promise due to significant advantages such as improved stability and silencing efficacy. Additionally synthetic siRNAs have reduced side effects as they can be chemically modified to prevent unintended immunostimulatory effects and also block sequence mismatches with unintended targets (Patil et al., 2014; Pai et al., 2005). Due to the specificity of RNAi, siRNA has the potential to be developed into a drug with great therapeutic applications in cancer. Currently it has already been used in cancer research to rapidly identify key molecules in cellular pathways in cancer. But RNAi technology can be refined to target key molecular pathways for cancer therapeutics. This led to significant data on the anti-proliferative effects in cell-culture systems or in preclinical animal models. However existing challenges lie in incomplete gene suppression and non-specific in vivo delivery causing side effects (Patil et al., 2014; Pai et al., 2005).

1.2. SiRNA against cancer targets

RNAi techniques can be employed against cancer targets that govern uncontrolled cell proliferation. Examples of such targets are cyclin dependent kinases (CDKs), insulin growth factors (IGF), vascular endothelial growth factors (VEGF) and anti-apoptotic factors. Cyclins and CDKs strictly regulate checkpoints within the cell cycle. Therefore overexpression of Cyclins could disrupt the cell cycle contributing to the development of cancer. Cyclin B1 has been linked to cancers such as renal cancer, prostate adenocarcinoma and breast cancer. siRNAs have been used in in vivo trials to silence expression of cyclin B1 for prostate and lung cancer (Resnier et al., 2013). Unregulated proliferation is a hallmark of cancer cells, which is caused by a positive balance of proliferative signals and acquisition of replicative immortality. Proliferation signals are generated by growth mediators like insulin growth factor (IGF), they activate intracellular cascades which promote cell proliferation, division and survival. This generates a suitable growth environment for cancer cells (Niepel et al., 2014). Disruption to cell death pathways are a critical step in cancer development, apoptotic regulators such as Bcl-2 proteins often determine cancer progression. The acquisition of cell death resistance mechanisms by cancer cells like the overexpression of anti-apoptotic Bcl-2 family members occurs in cancers such as leukaemia and myeloma. Angiogenesis is a critical factor for cancer progression, tumour growth requires a rich vascular supply to provide it with nutrients. Without angiogenesis, cancer growth would be limited to 2 mm in diameter (Resnier et al., 2013). Therefore tumour growth could be controlled by inhibiting the angiogenic mechanism promoted by vascular endothelium growth factors (VEGFs) (Carmeliet, 2005; Cao, 2014).

1.3. Concerns of siRNA application in cancer

Despite the promising nature of siRNA as a cancer drug, the therapeutic application of siRNAs has raised safety concerns, reports have underscored potential drawbacks. Differences in oncogenic mRNA expression levels between various cancer cells and also non-cancerous cells poses a challenge for developing a suitable therapeutic dosage without resulting in side effects (Gomes-da-Silva et al., 2014). The possible inhibition of tumour suppressive mRNA by siRNA could lead to spontaneous cancer development. Additionally the siRNA could gain entry into non-target cells causing undesired off target effects. Acquiring of resistance against siRNA by tumours is a cause for concern, despite the current effectiveness against tumours. Therefore key roles in cancer resistance progression need to be characterized so as to predict the outcome of siRNA treatment (Deng et al., 2014). The foreign nature of siRNA could provoke an immune response by the body's immune system to eliminate the siRNA and prevent the targeted localization of siRNA (Li et al., 2014). Protein with a high turn-over rate or a long half-life will limit the utility of siRNA as a tool for appropriate knock down. This is due to the siRNA targeting the mRNA used to synthesise the oncogenic protein but it does not directly reduce the amount of existing oncogenic protein (Resnier et al., 2013).

1.4. SiRNA cancer therapeutic strategy

The main strategy employed in siRNA therapeutics in the context of cancer is a loss-of-function approach. This is achieved by limiting or preventing target protein expression within the cells thereby altering the proliferation of cancer cells. Another advantage siRNA possesses is that it is not incorporated into DNA, thus it does not permanently modify the genome. Hence siRNA treatment can easily be stopped and controlled at any point, therefore fulfilling a critical factor for regulatory and safety considerations (Resnier et al., 2013). Currently the high efficacy of siRNA is limited by its delivery methods, hence improvements to the specificity and efficacy of current delivery systems is necessary before clinical applications (Karnati et al., 2014). Thus the focus of this review will be on nanoparticles delivery systems which are able to specifically and efficaciously deliver siRNA to cancer cells thereby silencing their oncogenic mRNA.

2. Roles of nanoparticles

Limitations to clinical application of naked siRNA drugs in oncology exist because of their physicochemical properties (Chen, 2011; An et al., 2015). The large molecular weight and polyanionic nature of siRNA limits its' passive uptake by cells. In addition extracellular

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