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Research review paper

Nanocarriers for microRNA delivery in cancer medicine

I. Fernandez-Piñeiro [a], I. Badiola [b], A. Sanchez [a,c,*]

[a] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Santiago de Compostela (USC), Campus Vida, 15782 Santiago de Compostela, Spain
[b] Department of Cell Biology and Histology, Faculty of Medicine and Odontology, University of Basque Country, B° Sarriena, s/n, 48940 Leioa, Spain
[c] Genetics and Biology of the Development of Kidney Diseases Unit, Sanitary Research Institute (IDIS) of the University Hospital Complex of Santiago de Compostela (CHUS), Travesía da Choupana, s/n, 15706 Santiago de Compostela, Spain

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ABSTRACT

The number of deaths caused by cancer is expected to increase partly due to the lack of selectivity and undesirable systemic effects of current treatments. Advances in the understanding of microRNA (miRNA) functions and the ideal properties of nanosystems have brought increasing attention to the application of nanomedicine to cancer therapy. This review covers the different miRNA therapeutic strategies and delivery challenges for its application in cancer medicine. Current trends in inorganic, polymeric and lipid nanocarrier development for miRNA replacement or inhibition are summarized. To achieve clinical success, in-depth knowledge of the effects of the promotion or inhibition of specific miRNAs is required. To establish the dose and the length of treatment, it will be necessary to study the duration of gene silencing. Additionally, efforts should be made to develop specifically targeted delivery systems to cancer cells to reduce doses and unwanted effects. In the near future, the combination of miRNAs with other therapeutic approaches is likely to play an important role in addressing the heterogeneity of cancer.

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* Corresponding author at: Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Santiago de Compostela (USC), Campus Vida, 15782 Santiago de Compostela, Spain.
E-mail address: alejandro.sanchez@usc.es (A. Sanchez).

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1. Introduction

1.1. Limitations of current cancer therapies

Cancer consists of a group of diseases characterized by uncontrolled division of abnormal cells that can invade and spread to other organs to form metastases. Neoplastic diseases exhibit distinctive capabilities such as proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan and Weinberg, 2011). Cancer is the second cause of death in developed countries and is associated with aging of the population and lifestyle (World Health Organization, 2016). The number of deaths caused by cancer was estimated to be 8.2 million in 2012, corresponding to 13% of all deaths. Although approximately two-thirds of cancer cases are cured due to advances in diagnosis, health care and treatment, the number of deaths is expected to increase. The lack of selective delivery of current treatments and the consequent systemic toxicity are among the major reasons for this trend (Wicki et al., 2015).

Radiotherapy and surgery are the most effective treatments for local and non-metastatic tumours, whereas chemotherapy, hormone and biological therapies are currently used for the treatment of metastatic cancers (Perez-Herrero and Fernandez-Medarde, 2015). However, despite significant progress in cancer treatments, the low selectivity, undesirable systemic effects and dose-limiting toxicity of current treatments make them nonspecific and non-ideal therapeutic approaches (Chabner and Roberts, 2005).

1.2. Nanomedicine in cancer treatment

Recent advances in nanomedicine applied to cancer therapeutics may help to overcome the existing limitations of antineoplastic drugs. Nanomedicine includes the design and development of nanoscopic delivery vehicles and diagnostic agents. These delivery systems can improve drug stability, increase the circulation time and selectively accumulate at the tumour site (Dawidczyk et al., 2014; Xu et al., 2015). Their nanometric size facilitates accumulation preferably at the tumour site due to the enhanced permeability and retention effect (EPR). The EPR effect is based on the presence of fenestrated blood vessels in the tumour, leading to extravasation of nanocarriers through a passive mechanism. Additionally, active targeting can be achieved through functionalization of the nanosystems with specific ligands for receptors on target cells.

Furthermore, current progress in understanding the molecular pathways and functions of cancer have enabled the identification of new targets and the development of novel therapeutic strategies. Hence, the finding of specifically altered signalling networks in cancer cells and the ideal properties of nanosystems have brought increasing attention to the application of nanomedicine to cancer treatment. A wide range of materials has been employed in the synthesis of nanocarriers and can be grouped into inorganic, polymer and lipid-based materials. In this review, we will cover nanosystems for microRNA (miRNA) delivery developed to date for cancer therapy.

2. MicroRNA

2.1. MicroRNA mechanism

RNA interference (RNAi) is an evolutionarily conserved method of gene expression regulation. RNAi is based on a post-transcriptional pathway triggered by a double-stranded RNA (dsRNA) that leads to sequence-specific silencing of a messenger RNA (mRNA) (Olson et al., 2008). RNAi was discovered by Fire and Mello in 1998 (Fire et al., 1998) and included endogenous (miRNA) or exogenous (siRNA and shRNA) RNAs. Gene silencing occurs when the double-stranded RNA molecules incorporate into the RNA-induced silencing complex (RISC). Then, the guide strand or anti-sense strand guides RISC to the complementary or near-complementary region of the target mRNA (Wang et al., 2011). miRNAs are only partially complementary to their target mRNAs and result in their degradation or translational inhibition, whereas siRNAs and shRNAs bind completely to and cleave the complementary strand (Rao et al., 2009; Davidson and McCray, 2011; Deng et al., 2014b). Toxicity associated with siRNA and shRNA overexpression is being debated; however, miRNA therapeutics seem to be safer and do not compromise the gene knockdown efficacy (Boudreau et al., 2009; Wang and Gao, 2014; Fellmann and Lowe, 2014).

Functional miRNAs are produced from the cleavage of pre-miRNAs in the cytoplasm. Mature miRNAs are 20–23 base pair double-stranded molecules comprised of a guide and a passenger strand that is released after loading into RISC, as shown in Fig. 1. Due to the ability of the miRNA to inhibit gene expression by partial complementarity to the mRNA, one miRNA can bind to different mRNAs and thus affect the expression of multiple genes.

2.2. MicroRNAs and cancer

The use of miRNAs for cancer therapy is based in the finding that miRNA expression is deregulated in cancer tissues and the ability of miRNAs to target multiple genes and alter cancer phenotypes (Garzon et al., 2010; Lam et al., 2015). Cancers are complex diseases involving deregulated expression of multiple genes, whereas miRNAs can modulate different disease pathways and increase the chances of eliminating the cancer. Moreover, distinctive miRNA expression profiles have been associated with specific cancer types, allowing for the discrimination and identification of poorly differentiated tumours (Lu et al., 2005; Volinia et al., 2006). Thus, miRNAs have shown relevant clinical utility for cancer therapeutics and diagnosis.

2.3. MicroRNA therapeutic strategies: sense and antisense microRNAs

In neoplastic diseases, miRNAs can be downregulated when they function as tumour suppressors or overexpressed when they function as oncogenes. Hence, two therapeutic approaches are currently being used to modulate miRNA functions: restoring miRNA activity using a synthetic miRNA and inhibiting the function of a miRNA through *anti*-miRNA oligonucleotides.

In situations where miRNAs are down-regulated, replacement therapy with miRNA mimics is used to restore miRNA levels and their tumour suppressive properties. Because the objective of this replacement therapy is to accomplish biological functions that are identical to the endogenous miRNAs, miRNA mimics should be loaded onto RISC to silence their target mRNAs. For this reason, double-stranded miRNA mimics are preferred over single-stranded mimics because the duplex structure has been found to facilitate RISC loading and thereby enhance the gene silencing efficacy (Bader et al., 2011).

In the case of overexpressed oncogenic miRNAs, the most widely used strategy is based on the use of miRNA antagonists to inhibit miRNA expression. The most common antisense approach is the use of single-stranded oligonucleotides that are partially or completely complementary to the target miRNA. The complementary binding of the antagonist to the endogenous miRNA prevents its processing by RISC. These antisense oligonucleotides (known as *anti*-miRNAs) are chemically modified to increase their binding affinity for the miRNA (van Rooij and Kauppinen, 2014). Accordingly, miRNAs could act as therapeutic agents or as therapeutic targets (Chen et al., 2015).

2.4. Challenges in microRNA delivery

Similar to other therapeutic oligonucleotides, miRNA delivery is a major challenge because naked miRNAs are quickly degraded by nucleases and cleared *via* renal excretion. Moreover, RNA administration may induce innate immune responses, leading to unwanted toxicities. In