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Polycation-based nanoparticles for RNAi-mediated cancer treatment

Borja Ballarín-González, Morten Frendø Ebbesen, Kenneth Alan Howard *

Interdisciplinary Nanoscience Center (iNANO), Department of Molecular Biology and Genetics, University of Aarhus, Aarhus, Denmark

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ABSTRACT

Cancer disorders exhibit an increasing high global incidence, in part, to an aging population with a high socio-economic burden. The cellular transition from normal to malignant state is linked to deregulated gene expression. The discovery of microRNA-mediated cellular regulation by the RNA interference (RNAi) pathway and the possibility to engage this pathway with exogenous triggers such as small interfering RNA (siRNA) could offer a new paradigm in anti-cancer intervention with RNAi-based therapeutics. The potential to silence the expression of any cancer-relevant protein with high selectivity promotes RNAi therapeutics as a more effective and safer treatment to traditional approaches. This combined with microRNA-based tumour profiling could pave the way for personalised approaches based on the genetic characteristics of the individual. Clinical translation of this technology, however, depends on the development of systems for effective delivery of the molecular medicine to the target site. Polycation-based nanoparticles (termed polyplexes) constitute an attractive platform for RNAi therapeutic delivery due to flexibility and versatility in design to overcome extracellular and intracellular barriers. In this review we focus on pre-clinical and clinical studies using polycation-based nanocarriers for RNAi mediated anti-cancer intervention after intratumoural or intravenous administration. Potential RNAi targets are highlighted and special attention is given to the enhanced permeability and retention (EPR) effect commonly cited at the predominant mechanism of delivery after systemic administration. The cyclodextrin polymer-based system now in clinical trials offers optimism that polyplexes may potentially be used for RNAi-mediated cancer intervention in the clinic.

1. Introduction

Cancer is generally defined as a complex group of disorders characterised by alterations in cell physiology that collectively drive malignant growth. Accumulation of genetic mutations and epigenetic alterations [1] have been linked to the acquisition of certain properties or traits that determine malignant cell transformation (for a comprehensive review refer to [2]). This conversion from normal to malignant cells is ultimately linked to deregulated gene expression.

Cancer disorders exhibit an increasing high incidence in the Western world due to an aging population with a high socio-economic burden. In Europe, 3.45 million new cases of cancer and 1.75 million cancer-related deaths have been estimated in 2012 [3] with breast, colorectal, prostate and lung cancers accounting for half of the overall incidences [3].

Advances in molecular and cell biology have allowed a greater understanding of malignant cell transformation and tumour growth fuelling the development of new therapeutic strategies. As opposed to the traditional testing of more or less randomly selected drugs, anti-cancerous compounds have been developed through the rational design of inhibitory molecules. Representative examples are the targeting of growth factors or downstream signalling pathway proteins with small molecule inhibitors [4–7] and monoclonal antibodies [8–11]. Understanding of the molecular pathways underlying transformation have not only contributed to the development of new therapeutics, but also, permitted a better sub-classification of the individual tumours based on their genetic characteristics. This knowledge is fundamental for the identification of optimal therapeutic approaches based on predicted drug response and toxicity, allowing a more personalised healthcare. Tailored oncologic intervention not only offers increased therapeutic efficacy and safety, but also, may reduce overall costs by avoiding unnecessary or inefficient therapies.

The discovery of miRNA-mediated cellular regulation by the RNAi pathway and the possibility to engage this pathway with exogenous triggers such as small interfering RNA (siRNA), may pave the way for personalised anti-cancer interventions with RNAi-based therapeutics.

* Corresponding author. Address: Aarhus University, Gustav Wieds Vej 14, DK-8000 Aarhus C, Denmark. Tel.: +45 87155831; fax: +45 87154041.
E-mail address: kenh@inano.au.dk (K.A. Howard).

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1.1. RNAi pathway

RNA interference (RNAi) is a fundamental process that in higher eukaryotes permits a fine-tuned regulation of cellular gene expression through post-transcriptional silencing [12]. This activity is mediated by endogenous small non-coding RNA species known as microRNA (miRNA) [13], that upon incorporation into an RNA-induced silencing complex (RISC) mediate translational repression of the targeted mRNA (Fig. 1). As multiple mRNAs present conserved target sequences for different miRNAs, miRNA expression allows for an elaborate and complex combinatorial control of cellular gene expression.

MicroRNAs are transcribed by RNA polymerase II as long primary miRNA (pri-miRNA) that are then processed by the RNase III-type Drosha into 50–75 nt stem loop precursor miRNA (pre-miRNA). Following an exportin 5-dependent transport into the cytoplasm [14], pre-miRNA are further cleaved by Dicer into 21–23 nt double stranded RNA (dsRNA), the matured miRNA, which

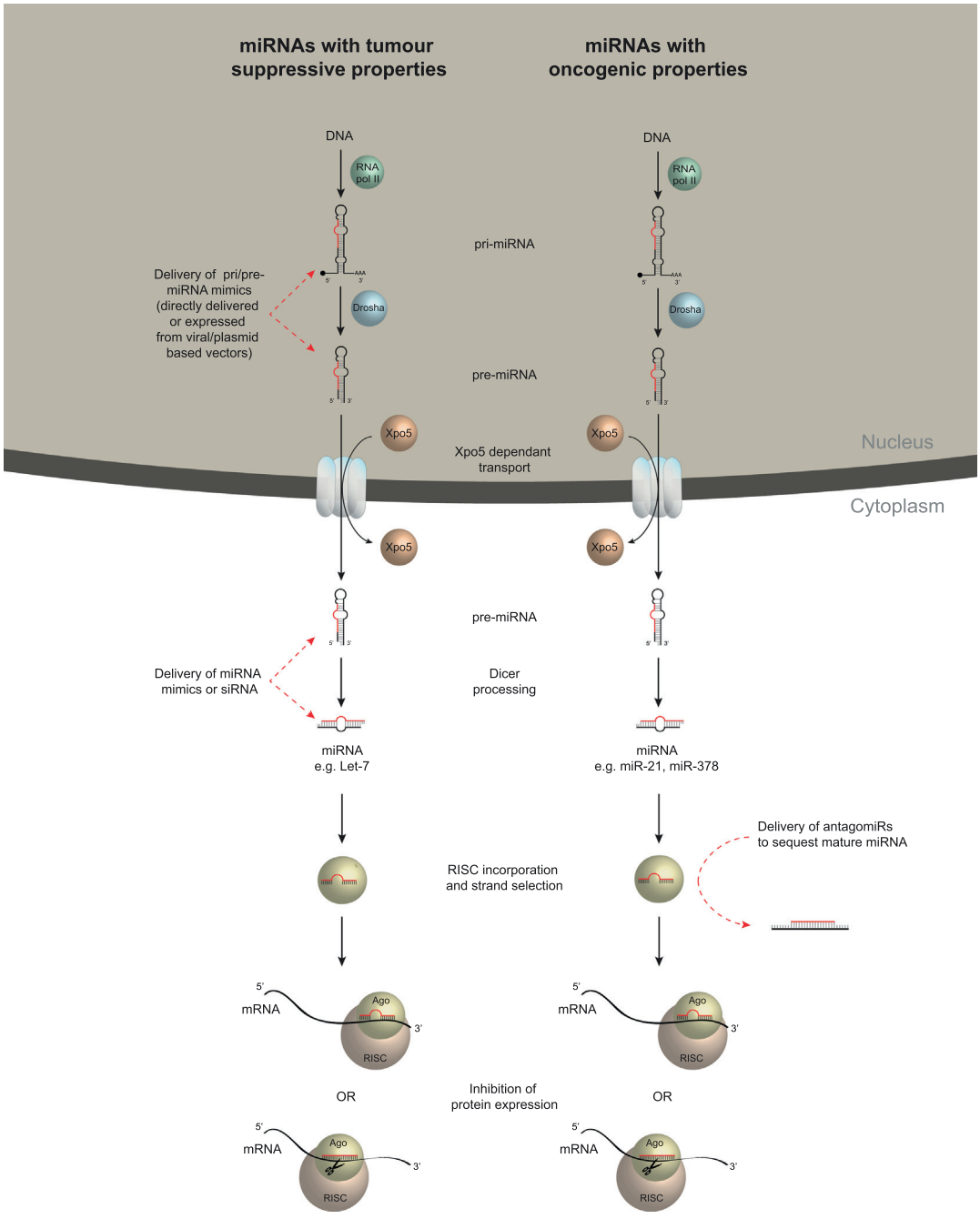

Fig. 1. Regulation of gene expression through the miRNA pathway Incorporation of mature miRNAs into RISC results in inhibition of protein expression either through translational repression or mRNA cleavage depending on a partial or total complementarity between the guide strand and the targeted mRNA. This regulation can promote maintenance of cellular homeostasis (miRNAs with tumour suppressive properties) or facilitate tumour development (oncogenic miRNAs). Mature miRNAs are generated through the processing of pri-miRNA into pre-miRNA and the subsequent cleavage into ~21 nt in length duplex RNA. These processing steps are mediated by the nuclear and cytoplasmic endoribonucleases known as Drosha and Dicer, respectively Dashed red arrows indicate potential anti-cancerous therapeutic intervention approaches at different levels of the pathway. Abbreviations: RNA pol II = RNA polymerase II; pri-miRNA = primary miRNA; pre-miRNA = precursor miRNA; Xpo5 = Exportin 5; RISC = RNA induced silencing complex (Graphic by Morten Jarlstad Olesen).

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