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Angiogenesis regulation by nanocarriers bearing RNA interference☆

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ABSTRACT

Since the approval of bevacizumab as anti-angiogenic therapy in 2004 by the FDA, an array of angiogenesis inhibitors have been developed and approved. However, results were disappointing with regard to their therapeutic efficacy. RNA interference approaches offer the possibility of rational design with high specificity, lacking in many current drug treatments for various diseases including cancer. However, *in vivo* delivery issues still represent a significant obstacle for widespread clinical applications. In the current review, we summarize the advances in the last decade in the field of angiogenesis-targeted RNA interference approaches, with special emphasis on oncology applications. We present pro-angiogenic and anti-angiogenic factors as potential targets, experimental evidence and clinical trials data on angiogenesis regulation by RNA interference. Consequent challenges and opportunities are discussed.

Contents

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1. Introduction

Angiogenesis is a crucial step in tumor development, as without the supply of oxygen and nutrients, tumors will not grow in mass nor be able to send metastatic cells. Therefore, targeting specific factors that contribute to the angiogenic process has a preventive and therapeutic anticancer potential. Many anti-angiogenic drugs have been developed in the last few decades; some of them were approved for clinical use [1–3]. Endothelial cells (ECs) are much more genetically stable and less likely to develop drug resistance than tumor cells [4]. Consequently, anticancer therapeutic agents targeting ECs are expected to be more effective than approaches targeting a tumor cell that might quickly develop an escape mechanism. However, despite the wide variety of anti-angiogenic agents, results were disappointing with regard to their therapeutic efficacy. Major challenges still need to be overcome in order to develop anti-vascular strategies, with an improved overall anti-cancer efficacy [5–8].

Angiogenesis is essential not only for cancer development, but also for other biological processes. Therefore, abnormal pathological angiogenesis is a common denominator of other *circa* 70 diseases. For example, excessive angiogenesis can be found in diabetes, age-related macular degeneration (AMD), arthritis and inflammation, while impaired angiogenesis can be found in conditions of myocardial infarction and ischemia [9,10]. Consequently, angiogenesis regulators have an immense therapeutic potential that exceeds cancer therapy.

The human genome project [11,12] has revolutionized our understanding of the molecular basis of health and disease. Since then, modifying expression patterns of specific illness-related genes is no longer science fiction, but a promising approach for the treatment of a wide variety of pathologies. We hereby focus on RNA interference (RNAi), a relatively new approach, nominated by the Science journal in 2002 as the 'breakthrough of the year' [13]. In fact, the discovery of RNA interference was the basis for the Nobel Prize in Physiology and Medicine awarded in 2006 to Andrew Z. Fire and Craig C. Mello [14] (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2006/press.html). Since then, the number of publications utilizing this novel technology has increased exponentially, leading to a better understanding of the RNAi mechanism and to the discovery of potential therapeutic applications.

In this review, we will focus on pro- and anti-angiogenic targets that can be inhibited by RNAi in order to return the physiological balance. We will discuss some of the advantages of silencing these factors as well as the challenges and pitfalls that still need to be overcome, including the vectors utilized for delivery of double stranded RNA molecules.

2. RNA interference

RNAi is based on the interaction of a short RNA strand with messenger RNA (mRNA) due to a sequence homology, resulting in translational inhibition.

2.1. Short interfering RNAs (siRNAs)

Short interfering RNAs (siRNAs) modulate the expression of specific genes, and therefore, can be used to regulate overexpressed or mutated genes identified as key contributors to diseases. RNAi is initiated by the Dicer enzyme, which processes double-stranded RNA into ~22-nucleotide siRNA. The siRNA is incorporated into a multicomponent nuclease, RISC (RNA-induced silencing complex), which is activated from a latent to an active form by unwinding of the siRNA duplex. The activated RISC then uses the unwound siRNA as a guide to select the matching mRNA. The mechanism of RNAi is illustrated in Fig. 1 and described in more detail in several reviews [15,16].

2.2. MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are an evolutionarily conserved group of siRNAs. miRNAs are transcribed first as long primary miRNAs (pri-miRNAs), mainly from intergenic or intronic regions by RNA polymerase II. The microprocessor complex, which its main component is the RNase III enzyme Drosha, processes long pri-miRNAs into short hairpins called precursor miRNAs (pre-miRNAs) [17,18]. The resulting pre-miRNAs are exported into the cytoplasm [19,20], where they are processed by RNase III Dicer into mature miRNAs [21]. The miRNA duplex generated is rapidly loaded to the RISC complex, where selection of the more stable strand occurs [22]. The resulting small RNA modulates gene expression by partially base-pairing with target mRNA sequences, generally in their 3′-untranslated region (3′UTR), thereby repressing translation and/or degrading the mRNA [23,24] (Fig. 1).

Because they do not integrate into DNA, siRNA and miRNA do not lead to genome modifications, an important parameter for regulatory and safety considerations. To date, numerous proteins have been silenced by siRNAs and miRNAs embedded into a variety of delivery systems as therapeutics for cancer and other pathologies based on cell cycle, apoptosis, proliferation and angiogenesis pathway studies [25–29].

We will hereby review the most recent approaches carried out to regulate angiogenesis by siRNA or miRNA, aiming to return the physiological balance (Fig. 2).

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