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## miRNAs as targets for cancer treatment: Therapeutics design and delivery★

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MicroRNAs (miRNAs) are a class of post-transcriptional gene expression modulators. In the past two decades, over 1500 human miRNAs were discovered. Each miRNA controls hundreds of gene targets through imperfect complimentary miRNA–mRNA binding. These small non-coding RNAs regulate various biological processes, including cell growth, proliferation, differentiation, and cell death.

The correlation of miRNA deregulation and cancers was initially demonstrated by transcriptional regulation of miRNAs by oncogenes and tumor suppressor genes. Later, genetic evidences also indicated the amplification, deletion, or epigenetic regulation of miRNAs in cancers. Depending on miRNA function, they are classified as tumor suppressors and oncomiRs. Tumor suppressor miRNAs are responsible for the inhibition of oncogenes. Downregulation of tumor suppressor miRNAs leads to tumor development and progression. OncomiRs refer to miRNAs over-expressed in cancer cells and function as inhibitors of tumor suppressor genes. Upregulation of oncomiRs initiates tumor growth and accelerates cancer development.

Abnormal expression of miRNAs not only leads to the activation of signal pathways related to tumor initiation and progression, but also promotes cancer metastasis and resistance. These issues are discussed in several reviews with different focuses. Wu and associates discuss the role of miRNAs in regulating NF- $\kappa$ B signaling circuits of cancers. Elevated NF- $\kappa$ B levels in various cancers are often correlated with cancer development and their resistance to therapies. Therefore, miRNAs that regulate NF- $\kappa$ B as well as its upstream and downstream signaling pathways have shown great potential as targets for therapeutics design. Batra and associates discuss the clinical implication of miRNAs in the pathogenesis, diagnosis, and therapy of pancreatic cancer. They summarize the role of miRNAs in regulating multiple critical signaling pathways, including KRAS, p53, p16, TGF- $\beta$ /SMAD signaling, and Sonic Hedgehog signaling. The application of miRNAs for pancreatic diagnosis and therapeutics design is also discussed. Mahato and associates review the

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application of miRNAs for the treatment of pancreatic ductal adenocarcinoma (PDAC) and strategies to overcome delivery challenges. The levels of miRNAs are significantly changed during the epithelial-to-mesenchymal transition (EMT). miRNAs also have altered expression in drug-resistant tumor cells, indicating the roles of miRNAs in the development of drug resistance. miRNAs involved in drug resistance are also related to cancer stem cells (CSCs) and EMT regulation. The critical roles of miRNA in desmoplasia, chemoresistance, and EMT of PDAC are summarized in this review. This review also discusses various strategies for *in vivo* delivery of miRNA therapeutics which is the major challenge for their clinical translation. Garofalo and Croce summarize the critical role of miRNA in maintaining cancer stem cells. Yang and associates discuss the application of miRNAs as targets for therapeutics design and biomarkers for diagnosis in hepatocellular carcinoma.

Because of critical roles of miRNAs in cancer pathogenesis, miRNAs not only become promising targets for cancer therapy but show great potential as biomarkers for cancer diagnosis. The application of miRNAs for cancer diagnosis is reviewed by Guofeng Cheng. In this review, the use of circulating miRNAs as diagnostic and prognostic biomarkers in various cancers is discussed. In addition, methods and strategies for the identification of circulating miRNAs are also introduced.

The development of bioinformatics technologies provide useful tools to analyze data generated from high throughput methods. This topic is discussed by Banwait and Bastola. Computational approaches are useful for predicting miRNA targets. Bioinformatics can also provide tools to study human cancers. Its application in pancreatic cancer research is highlighted as a case study.

Inhibition of oncogenic miRNAs can be achieved using antagomirs (which are antisense single-strand oligonucleotides), or miRNA sponges (which are mRNAs with multiple targeting sites for specific miRNAs). Wang and associates review the use of miRNA sponges to inhibit miRNAs in cancers. This review summarizes the various aspects of miRNA sponge technology, including miRNA sponge design, expression cassette, and delivery vector selection. miRNA sponge can simultaneously inhibit the expression of a family of miRNAs. Therefore, it will be a useful tool for understanding the roles of miRNAs in cancer developments as well as a therapeutic approach.

As *in vivo* delivery of macromolecule miRNA continues to be a significant challenge, alternative approaches are being explored for miRNA-targeted therapy. The use of small molecule drugs targeting miRNAs for cancer therapy is an excellent example of such efforts. Small molecule drugs are more stable and have less delivery challenges compared to macromolecules. This topic is reviewed by Calin and associates. In this article, authors discuss the use of small molecule inhibitors of specific miRNAs (SMIRs) for treating cancers. High-throughput approaches have been used for more efficient screening of SMIRs. The discovery history of several validated SMIRs is reviewed at the end.

The development of miRNA therapeutics and their applications in the clinic for cancer therapy is hampered due to many challenges in delivering these molecules into target cancer cells or tissues. The delivery of miRNAs remains a significant technical obstacle in turning

miRNAs into therapeutics. Depending on the miRNA targets and intended disease for treatment, various delivery approaches can be utilized including but not limited to: (1) chemical modification of antagomirs; (2) synthetic carriers for miRNA delivery; and (3) miRNA expression viral vectors. Chen et al. discuss the challenges for *in vivo* delivery of miRNAs in the context of cancer therapy. The understanding of these challenges is helpful for the rationale design of various delivery systems including chemical modifications, viral vectors, and non-viral systems. Non-viral systems are quite promising for clinical applications. Huang and associates summarize the use of different synthetic carriers for miRNA delivery. The targeted delivery systems, which utilize either active or passive targeting strategies, are most attractive for cancer therapy. The review by Golzio and associates on electro-delivery of oligonucleotide is an excellent example of using physical method for siRNA and antimiR delivery. Electroporation can deliver antimiRs to specific tissues, enhance cellular uptake and bypass many delivery obstacles. João Conde et al. discuss the use of nanomaterials for miRNA sensing and for the delivery of therapeutic miRNA.

Due to the heterogeneous nature of cancers, combination therapy is often used to improve the therapeutic outcome. The combination of therapeutic miRNAs and small molecule drugs can target multiple signaling pathways or therapeutic targets, and thus can have synergistic or additive effects. This combination strategy can enhance therapeutic effects by promoting apoptosis and autophagy, reverting EMT, suppressing angiogenesis, and downregulating drug resistance transporters. Despite these advantages, the combination therapy has additional delivery challenges. Therefore, some specific delivery approaches have been investigated for co-delivery of small molecules and miRNAs in combination therapy. This topic is reviewed by Tan and associates.

In summary, this theme issue discusses various aspects of miRNA as cancer therapeutics and focuses on the design of delivery systems of miRNAs and their use as therapeutics. The research of miRNA-based cancer therapeutics has made significant progress in the past few years. However, many issues still have not yet been fully addressed. We would like to thank all the contributors of this issue of the *Advanced Drug Delivery Reviews*. We hope that their outstanding contributions provide greater insight into the current status, achievements, and challenges of miRNA-based therapeutics. We hope this issue provides stimulation for innovative approaches and further development, which will help us in turning miRNAs into therapeutics and diagnostic agents.