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MicroRNA Potential Application in Disease Therapy

MicroRNAs are small, non-coding RNA molecules that suppress gene expression both by inhibiting protein translation and promoting mRNA cleavage. Since their exploration, a large amount of miRNAs have been described and extraordinary progress has been made toward finding their function as well as their uses in research and clinical practice**.**

Expanding knowledge about the role of microRNAs in biology and their dysregulation in many diseases has prompted scientists to investigate their potential use in disease therapy. There were two strategies employed. It could be either miRNA restoration therapy in which a down-regulated or non-functional miRNA would be supplied by a synthetic oligonucleotide or miRNA inhibition therapy where the over-expression of an increased miRNA would be inhibited by antagonists.

MicroRNA mimics are double-stranded RNA oligonucleotides exactly copying the mature miRNA duplex in which only the guide strand will target mRNAs whilst the passenger strand will be degraded. However, in some case, strand bias could be introduced into the mimic in which the passenger strand could target mRNAs leading to considerable side-effects. Natural miRNA efficacy is normally limited for therapeutic purpose as they are easily degraded by RNAese and/or they could stimulate the innate immune system through activating Toll-like receptors. This problem could be addressed through modifying either RNA phosphodiester or ribose sugar backbones of the synthetic microRNA mimic. An appealing site for alteration is the 2` -OH position of the ribose sugar since it is not required for miRNA function and found to be attacked by several nucleases to catalyze RNA degradation. The most common modifications made to this position include 2`-O-methyl (2`-OMe) and locked nucleic acids (LNA

An anti-miRNA therapeutics aims to arrest the expression of miRNAs in the target tissues. This could be achieved through miRNA inhibitors, miRNA sponges, or small molecular miRNA inhibitors inhibiting of miRNA and mRNA interaction.

MicroRNA inhibitors, which are known as antagomirs, miRNA masks, and LNA miRNA inhibitors work by specifically binding to the desired miRNA to prohibit its interaction with targeting mRNA. The binding of miRNA inhibitor and their target miRNA to form RNA duplexes precedes to the deterioration of miRNAs by RNAese H. Similar to miRNA mimic, a microRNA inhibitor also requires chemical modifications to increase its stability and reduce immune response. Antagomirs and LNA miRNA inhibitor are both antisense oligonucleotides which are very complementary to the desired miRNA. The LNA miRNA inhibitors have the 2`-O and 4`-C atoms of the ribose ring hooked up through a methylene link, declining the elasticity of the ring and prompting the rigid conformation.

These modifications provide nuclease resistance and strengthen binding affinity of antimiRNAs to their targeting miRNAs. MicroRNA sponges are plasmids with numerous miRNA binding sites by which pairing and eventuating diminishing

the endogenous miRNAs. To enhance the lifetime of these sponges, the interacting sites are constructed to be not perfectly paired to the miRNA to prevent the dissection of the sponges by RNAse H (which recognizes DNA/RNA duplexes). Interestingly, the operating mechanism of miRNA sponges is not entirely manufactured as endogenous miRNAs sponges present as circular RNAs. For example, ciRS-7, a circular RNA, has 73 miR-7 binding cites in order to regulate miRNA-7 levels in neurons. The microRNA sponge has been an effective method for determining miRNA functions in vitro. For therapeutic utilizations, however, it becomes difficult because of safety and off-target effects created by exceeding exotic plasmids.

MicroRNA -based therapy is promising. However, there are many challenges associated with miRNA delivery limiting its efficacy. Systemic administration is utilized for drug delivery in pragmatic clinical application. However, miRNA mimics or inhibitors would be degraded by RNAse in the circulation even with chemical modification. Moreover, the miRNA could be taken up by other organs leading to non-specific effects. The dense, extracellular matrix in some tissues could also serve as a physicochemical barrier to prevent cellular entry of miRNA mimics or inhibitors. In addition, the negative charge of nucleic acids and relatively large molecular weight may prevent the passive diffusion of a miRNA or inhibitor through the anionic phospholipid bilayer membrane to enter the cytosol . If it was posted by endocytosis, endosomal liposomal trafficking could result in the microRNA being degraded in the lysosome compartment. Therefore, there is a need for a multifunctional delivery system to overcome all the miRNA delivery hurdles in order to exploit the benefits of miRNA-based therapy.

There are several methodologies for miRNA delivery including conjugation, virus associated delivery, and nanoparticles. Even though the virus-associated miRNA delivery approaches have been experimentally proven to be efficient for cancers, virus-related safety concerned have limited its clinical application for the moment and other non-viral delivery systems seem more promising. The conjugation system in which lipids or cell receptor targeting ligands are directly conjugated to a miRNA, is a good approach for miRNA delivery.

RG-125 (also known as AZD4076), RGLS5040 and RG-012 are antagomiRs targeting miR-103/107, miR-27, and miR-21, respectively. RG-125 and RGLS5040 aim to treat of nonalcoholic steatohepatitis, and cholestatic diseases, respectively, whilst RG-012 is for the fibrogenesis of organs associated with Alport syndrome. However, the development of these three was suspended.

The miR-29 family (miR-29a/b/c) is reported to decrease expression in fibrotic diseases in which the miRNA inhibits the buildup of the extracellular matrix. Interestingly, the miR-29 level could be restored by MRG-201 (also known as Remlarsen), a LNA RNA mimic delivered by intradermal injection. Similar to the miR-29 family, the miR-34 family (miR-34a/b/c) level could be rescued in several cancers, e.g., renal cell carcinoma, acral melanoma and hepatocellular carcinoma by MRX34, a double stranded RNA encapsulated into a liposome-formulated nanoparticle.

MRG-106 (Cobomarsen, a LNA antagomiRs) and MRG-107 (an antagonist) both target miR-155. Whilst MRG-106 aims for treating certain types of lymphoma

and leukemia, MRG-107 is for alleviating symptoms and extending survival associated with amyotrophic lateral sclerosis. However, only MRG-106 is in phase 2 while MRG-107 has not yet entered clinical trials. MRG-110 (a mixer of LNA and DNA antagomir entirely altered with phosphorothioate internucleotide bridges) target miR-92 in order to cure ischemic conditions such as heart failure.

Mesomir, is a miRNA mimic for substituting miR-16 which is repressed in various cancers such as malignant pleural mesothelioma. It has completed its phase 1 clinical trial and is following phase 2. ABX464 is a small molecular compound prompting the overexpression of miR-124 to reduce the feature of inflammatory colon in patients resisting to corticosteroids and anti-TNF biologics. It is in phase 2a and 2b clinical trial for Crohn's disease and ulcerative colitis, respectively.

in conclusion Although the potential of miRNA-based therapy is fascinating, much more needs to be addressed. Investigation of microRNA target genes and its functions are crucial for the outline of miRNA-based treatments in different human pathologies. The development of miRNA mimetics and miRNA inhibitors is a good selection for either functional recovery or antagonization of endogenous miRNAs. However, high doses of these exotic miRNA mimics and inhibitors could switch on the innate immune response, resulting in increased expression of numerous cytokines. In addition, many modifications are under investigated to increase stability of miRNA mimics or inhibitors during delivery. These problems need to be resolved for effective future application of miRNA-based therapies.