Micro-RNA Therapeutics in Cardiovascular Disease: Where does the Science Lie?

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Disclosures

- No relevant financial disclosures
- No off-label therapeutic discussion
Objectives

• Discuss *mechanisms* of micro-RNA (miRNA) inhibition of protein translation

• Introduce miRNAs as a new class of biomarkers in cardiovascular disease

• Review current and potential *applications* for miRNA technology in cardiovascular disease

• Highlight potential and known *adverse effects* of RNA technology in the treatment of cardiovascular disease
miRNA – Mechanisms for Repression

Evolutionarily conserved ncRNA approximately 20–22 nucleotides in length

Inhibit expression of native genes through direct binding to multiple mRNAs

May also induce RNA degradation when sequences match

miRNA Diversity and Plurality

To date, over 1880 unique human miRNAs have been identified

May target and inhibit hundreds-thousands of genes
miRNA – A Novel Class of Biomarkers

miRNAs are known to be released from dying cells.

miRNAs are also actively secreted from multiple cell types.

Can miRNA levels in the blood detect and/or predict cardiovascular disease?

mRNAs are protected from RNAse and other forms of degradation:

- packaging in extracellular vesicles
- association with RNA-binding protein complexes
- in lipoproteins including HDL and LDL

Mechanisms that govern the release of miRNA into the extracellular space are incompletely understood.

Nature Reviews Clinical Oncology 8, 467-477 (2011)
Nature Reviews Clinical Oncology 11, 145–156 (2014)
Cardiovascular Disease and miRNA

miRNA expression patterns differ between healthy subjects and those with CVD and other cardiovascular diseases.

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- packaging in extracellular vesicles
- association with RNA-binding protein complexes
- in lipoproteins including HDL and LDL

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Biomarkers for CV Disease Risk Factors

- Cigarette Smoking
  - miR-126
  - miR-223

- Hypertension
  - miR-320
  - miR-208a/b

- Dyslipidemia
  - miR-122
  - miR-33

- Obesity/Sedentary Lifestyle
  - miR-26a
  - miR-222
Mipomersen: Lessons Learned from RNAi Technology

Mipomersen is a synthetic antisense RNA

Binds the ApoB mRNA

Prevents translation of the ApoB100 protein

nucleotides are linked with phosphorothioate linkages

capped with 2’-O-methoxyethyl-modified ribose

given as a weekly injection

Effective for sustained reduction in LDL-C

Flu-like reactions are relatively common

Relatively rare serious effects are seen over 2 years

(some elevations in ALT, nonspecific GI side effects, etc)
miRNA Therapeutics for Cardiovascular Disease

anti-miR therapies exist in Phase II clinical trials for patients with hepatitis C

miR-based therapies are currently in pre-clinical and Phase 1 trials for multiple illnesses, primarily malignancies

Cardiovascular diseases currently being investigated include post-MI remodeling, chronic heart failure and peripheral arterial disease

Mitchell, et al Pharmacology & Therapeutics (Sep 2016)
Miraversen: miRNA Therapy for Hepatitis C

Miraversen: an antisense modified oligonucleotide that inhibits miR-122

miR-122 binds HCV RNA and promotes translation

Inhibition of miR-122 reduced HCV viral load in initial trials with no significant side effects at 4 weeks of therapy.

Data courtesy of Santaris Pharmaceuticals, Inc
miR 15/195

MGN-1374

Inhibitor of miR 15/195

Preclinical animal trials show improvement in proliferation of cardiomyocytes post-infarction


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miR208

MGN-9103 is an inhibitor of miR-208a phosphorothiolated oligonucleotide
Potential Side Effects to miR Therapy

miRs are promiscuous molecules

prolonged exposure to anti-miR or pro-miR therapy may lead to numerous side effects

miR therapy is in its infancy
Conclusions

miRNAs inhibit translation of multiple gene targets leading to various effects throughout multiple systems.

Anti-miR therapy has been shown to be preliminarily effective in Phase 1-2 trials for limited indications (HCV).

The role of miR therapy in cardiovascular disease has yet to be clarified in humans, though a potential for therapeutic benefit exists based on animal trials.

The technology exists to alter miR activity and may prove to be a staple of therapy in the future for chronic cardiovascular disease.