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Cardiovascular Diseases and their Novel Therapeutic Interventions: A Literature Review

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Abstract

Introduction: Cardiovascular diseases (CVD) are responsible for millions of deaths worldwide every year and remain one of the main causes of death in low- middle-income countries. Current methods of treating CVD involve the use of lipid-lowering drugs although these patients continue to suffer from atherosclerotic disease risk. Novel RNA therapeutic strategies are being brought to light with the advancement in our understanding of cellular mechanisms and communication, however, these need to be evaluated critically before their clinical use.

Methods: Electronic literature databases such as PubMed and Google Scholar were used to access review papers and research studies done in the past 25 years. Studies most relevant to RNA cardiovascular therapeutics were used to study therapeutic interventions and their limitations.

Results: MicroRNAs (miRNAs), a subset of non-coding RNAs play an important function in cell-cell communication and microenvironment remodeling due to their role in cellular processes such as differentiation, proliferation, and apoptosis. Dysregulation of miRNA synthesis has been shown to drive disease pathology. Administration of the miRNAs downregulated during disease or silencing the activity of pathogenic miRNA can be used to establish the genetic composition of a healthy individual. Exosomes are cell-derived bilipid layer extracellular vesicles, 40-150 nm in size, which conduct paracrine signaling by carrying a cargo of mRNAs, non-coding RNAs, and proteins. They could be used as an efficient delivery method for miRNAs. Gene silencing therapies targeting the ApoCIII gene have emerged as novel therapeutic interventions to treating CVD with genome-wide association studies demonstrating enhanced cardioprotective function with ApoCIII deficiency. Gene silencing through miRNA delivery and antisense oligonucleotides reveals new avenues of CVD treatment.

Discussion: Novel therapeutics addressing miRNA dysregulation and gene expression regulation come with caveats that need to be addressed before they are prescribed. This review describes the role of the gene silencing interventions and the implementation barriers that delay their approval for use in treating heart disease.

Conclusion: The treatments and limitations addressed in this review suggest more studies are needed to determine the pharmacokinetic aspects of RNA drugs prior to establishing the use of RNA therapeutics along with conventional cholesterol-lowering drugs to ameliorate CVD risk.

Keywords: cardiovascular disease; therapeutics; atherosclerosis; microRNA; ApoCIII; triglycerides

Introduction

Cardiovascular diseases (CVD) remain the leading cause of death across the globe with about 17.9 million deaths in 2019 [1]. CVD risk factors include atherosclerosis, endothelial cell dysfunction, vascular inflammation, arterial remodeling, dyslipidemia, and obesity. CVD risk factors are driven by behavioral lifestyle choices such as unhealthy diet, physical inactivity, tobacco use, and excessive alcohol consumption [1,2]. Based on decades of research evidence showing the atherogenic role of high concentrations of triglycerides, current methods of treating CVDs involve statins, fibrates, PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors, and other lipid-lowering agents which reduce the risk of CVD along with lifestyle modifications [3]. Despite these therapeutic interventions, a multifactorial disease like CVD necessitates additional therapeutic modalities to target pathophysiological processes involved in pathogenesis.

While only less than 2% of the genome codes for proteins, non-coding sequences form a major part of the human genome. The non-coding sequences comprise microRNA (miRNA) and long non-coding RNAs. MiRNAs regulate gene expression by post-transcriptional regulation through blocking translation or protein degradation which will be the focus of our discussion. In contrast, long noncoding RNAs have diverse functions involving interactions with DNA, RNA, and proteins to regulate their function [4]. MiRNAs are 20-23 nucleotide long single-

stranded RNA sequences that play important roles in basic cellular functions such as differentiation, growth, proliferation, and apoptosis [5]. MiRNAs are attractive targets for cardiovascular therapeutics due to their stability, tissue-specific expression, and secretion, however, their renal clearance, delivery, and endocytosis by target tissues remain the major obstacles to overcome [6].

Another therapeutic intervention is the antisense oligonucleotide mediated silencing of the ApoCIII gene which is a member of the APOA1/C3/A4/A5 gene cluster known for its involvement in lipid metabolism [7]. The ApoCIII gene codes for a proinflammatory protein component of triglyceride (TG)-rich lipoproteins (TRLs). The encoded protein plays a role in the metabolism of these TRLs which include very-low-density lipoproteins (VLDL), high-density lipoproteins (HDL), and chylomicrons (TRLs produced in the intestine from dietary lipids). Chylomicron TRLS promote the secretion of VLDLs, inhibit lipoprotein lipase enzyme activity and delay catabolism of TRL remnants [8]. There is evidence that therapies like statins, fibrates and CEPT (cholesteryl ester transfer protein) inhibitors have shown a reduction in ApoCIII levels while lowering plasma triglyceride levels [9]. Since hypertriglyceridemia in patients with type 2 diabetes mellitus, obesity, and vascular endothelial cell activation/dysfunction such as in atherogenesis are strongly linked to ApoCIII metabolism, regulation of the ApoCIII gene offers a promising therapeutic approach to combat CVD.

Methods

A preliminary search was performed on the PubMed and Google Scholar databases for novel RNA therapeutic interventions in cardiovascular disease. The search criteria included (1) peer-reviewed articles published between 2000 – 2021 (2) relevance of research papers was determined by the presence of keywords such as cardiovascular therapeutics, cardiovascular diseases, and risk factors, prevention of cardiovascular diseases (3) peer-reviewed (4) published in English. The search was narrowed down to focus on miRNA therapeutics and ApoCIII gene silencing in CVD. RNA therapeutics in CVD and the function of ApoCIII were used as the search term on electronic literature databases such as Google Scholar, PubMed, ScienceDirect, and Directory of open access journals (DOAJ) to find relevant literature reviews and research studies. Sources were also selected from the citations of the relevant papers. CAARP (currency, authority, accuracy, reliability, purpose) test was used to evaluate the sources for bias.

Results

MicroRNA and Exosomes Therapeutics

Roles

MiRNAs regulate gene expression by binding to the 3′-untranslated region of their complementary target mRNAs and induce mRNA translation inhibition, or degradation [4]. Several recent studies have described miRNAs that contribute to the development and progression of CVD such as myocardial infarction (MI), fibrosis, heart failure, and atherosclerosis [4]. While cardiac hypertrophy is induced by overexpression of miR-195 [10], extracellular matrix (ECM) remodeling and fibrosis are induced by overexpression of miR-29 [10], miR-21 [11], and downregulation of miR-133 and miR-30 [12]. Atherosclerotic lesion development can be prevented through the maintenance of a proliferative reserve in endothelial cells by suppressing the Notch1 inhibitor - DlK1 through the expression of endothelial miR-126 [13]. miR-146a [14] and miR-181b [15] exert anti-inflammatory activities through the inhibition of NF-κB (Nuclear factor kappa B) signaling. These examples of miRNAs regulating CVD are promising therapeutic targets for clinical therapy. The goal of miRNA therapeutics is to restore the miRNA expression levels by two main approaches: overexpression of downregulated miRNAs and suppression of overexpressed ones. In other words, miRNA therapeutics requires oligonucleotides that mimic endogenous miRNA and suppress the mature miRNA by complementary binding of oligonucleotides that block the miRNA from inhibiting mRNA translation [6].

MicroRNA mimics are artificially synthesized double-stranded RNA molecules which are modified through chemical modifications and nucleotide changes to improve their stability [16]. Exposure to different nucleases in the system renders naked nucleotide sequences less efficient both in vitro and in vivo. The nucleotide sequences can be protected by using lipid-based vehicles, viral systems, and cationic polymerase as some of the main methods of RNA therapeutics delivery [6]. Lentiviral, retroviral, and genetic approaches to altering cellular concentrations of individual miRNAs involve the integration of a pre-miRNA sequence into the genome of a cell. This results in their encoded miRNAs following the same biogenesis pathway and mechanism of action as the endogenous miRNAs giving rise to more physiologically relevant outcomes [16]. Ma et al. [17] showed that treatment with miR-146a and miR-181b packaged in an E-selectin-targeting multistage vector (ESTA-MSV) reduced atherosclerotic plaque size in male apolipoprotein E-deficient mice fed a high-fat diet and ameliorated endothelial inflammation and atherosclerosis.

Exosomes, cell-derived lipid bilayer extracellular vesicles (EVs) have been endorsed in recent years for their role in both long-distance paracrine signaling and microenvironment communication through the transport of RNA and proteins between cells. EVs have most importantly been recognized for use in atherosclerotic progression [18]. In a study, Botts et al. discovered that the EV-derived miRNAs from patients with Abdominal Aortic Aneurysms (AAA) are involved in aneurysm pathogenesis via cell signaling and senescence pathways [19]. Interestingly, engineering exosomes to contain non-native miRNA mimics can offer the advantage of more stable,

efficient, and non-immunogenic delivery of their cargo due to their natural role in miRNA secretion and shuttling between different cells [18]. Wang et al. showed that systemic administration of extracellular nanovesicles (eNVs) derived from mesenchymal stem cells through electroporation to contain 315-fold miR-101a levels inhibited fibrosis and increased cardiac function in a mouse model of MI [20]. Additionally, artificial microRNAs (amiRNA) composed of a pri-miRNA scaffold and small interfering ribonucleic acid (siRNA) insert are being explored as a low toxicity, single administration, and stable substitute of the conventional RNA interference methods such as siRNA and small hairpin RNA [21].

The most studied miRNA inhibitors are antagomiRs, locked nucleic acid (LNA) anti-miRs, and miRNA sponges [4]. The basic concept of action for all the miRNA inhibitors is that the antisense molecules match the target miRNA in a complementary fashion and prevent base-pairing of the miRNA with its mRNA target, thus blocking the inhibitory function of miRNAs. These antisense molecules differ by their chemical modification and the efficiency of these miRNA inhibitors varies depending on the target miRNA [4]. Studies have shown that an LNA directed against miR-21 does not have beneficial effects but antagomiR treatment reduces cardiac fibrosis and hypertrophy [22]. In this study, LNA was complementary to nucleotides 2- 9 in miR-21 however, antagomiR was complementary to full-length miR-21 which explains the higher efficacy of the latter due to delayed excretion of oligonucleotides with a higher number of phosphorothioate bonds [22]. MicroRNA sponges are circular RNAs (CircRNAs) that sequester up to 10 miRNAs and repress the endogenous activity of multiple miRNAs at once [23, 24]. Lavenniah et al. constructed a circular miRNA sponge to target miR-132 and miR-212 known to drive cardiac hypertrophy. This sponge was delivered by an adeno-associated virus in vivo to cardiomyocytes of a mouse model of cardiac disease to show improvement of cardiac function and attenuation of heart failure progression [24]. Engineered CircRNAs thus offer immense potential as future therapeutics due to their low dose requirement and higher stability compared to current alternatives [24]. These strategies provide an efficient tool for harvesting the benefit of microRNA-based therapeutics in combating cardiovascular disease.

Limitations

In treating CVD, miRNA-based strategies along with exosome-based delivery of miRNA-based drugs offer exciting potential. Evidence of impediments to overcome include inefficient delivery, immunogenic responses, long-term effects, and subsequent off-target effects. MicroRNA therapeutics have several challenges to address despite being appreciated in theory. The "too many targets for miRNA effect" (TMTME) phenomenon which emphasizes that one miRNA targets several genes poses a significant challenge. MRX43, a miR-34a mimic in a phase I trial (NCT01829971) led to serious immune-related adverse events in 5 participants, therefore, causing the termination of the trial. Pathway analysis of miR-34a using KEGG Orthology-Based Annotation System (KOBAS), a web-based platform for pathway identification, showed that two immune-related pathways, namely cytokine signaling in the immune system and signaling by interleukins, were on the list [25]. Moreover, targeting the whole miRNA family by using LNAs may be beneficial as in the case of mir-15 inhibition on ischemic injury to enhance cardiac function but may not be suitable for all miRNAs such as miR-21 [22, 26]. Transfection of miRNAs or siRNAs to regulate gene expression typically suppresses target genes. Khan et al. showed that gene upregulation of nontarget genes can also occur in some cases from the "saturation effect" which is governed by the competition for intracellular small RNA processing machinery between the transfected si/miRNAs and the endogenous pool of miRNAs such as saturation of the RNA-induced silencing complex (RISC) [27]. The saturation effect must be considered to address the mRNA expression changes after miRNA perturbations to predict the miRNA target. All the various challenges discussed also require protected transport in blood, fine-tune dosing, and organ-specific targeting.

ApoCIII Gene Silencing

Roles

The ApoCIII gene plays important roles in other atherogenic processes such as endothelial dysfunction, inflammation, and coagulation [28]. Riwanto et al. showed that an increase in ApoCIII content in coronary artery disease (CAD) patients was associated with remodeling of the HDL proteome driving deterioration of anti-apoptotic effects of HDL [29]. ApoCIII activates the NF-κB pathway responsible for endothelial dysfunction and monocyte adhesion through increased expression of VCAM-1 (Vascular cell adhesion protein 1) and ICAM-1 (Intercellular Adhesion Molecule 1) in endothelial cells [30]. A prospective study found a positive correlation between higher levels of ApoCIII and increased thrombin generation exposing the patients to an increased risk of thrombosis [31].

A whole-exome sequencing study of 18,666 genes in each of 3734 European or African ancestry participants identified four mutations – loss of function, two alternative splice sites, and a missense mutation in the gene encoding ApoCIII. Interestingly, TG levels were 39% lower and the circulating levels of ApoCIII were 46% lower in carriers than in noncarriers. As a result, the risk of cardiovascular disease was lower in the carrier patients [32].

The currently used methods of lowering plasma TG levels are fibrates, omega-3 fatty acids, niacin, and statins [33]. The TG lowering mechanism in all these therapies directly or indirectly affect ApoCIII mRNA and ApoCIII protein products [34-38]. These observations and genetic

evidence emphasize the need to develop a method of ApoCIII gene expression modulation. Antisense oligonucleotides (ASOs), 8-20 nucleotide long RNA sequences, are designed to specifically target RNA leading to downstream modulation of mRNA translation [39]. Studies have shown successful antisense oligonucleotide inhibition of the ApoCIII gene in rodents, non-human primates, and humans to lower plasma TG levels [40, 41, 42]. The ApoCIII gene inhibition in a study done by Graham et al. resulted in cardioprotective effects such as reduced plasma TG levels, increased lipid remnant clearance, reduced VLDL particle composition, and enhanced HDL levels [40]. ASOs are distributed at therapeutic concentrations in most major organs, including the liver which is the key organ in lipid and lipoprotein metabolism [9]. Due to their solubility in normal saline and efficient delivery without excipients via subcutaneous, intravenous, topical, aerosol, intraventricular, and oral routes of administration, the ASO drugs offer a promising method for lowering TG levels [39]. Also, the half-lives of the ASOs range from 10 to 30 days due to slow endonucleolytic cleavage from tissues, in contrast to the daily dose of cholesterol-lowering pills [39]. Additionally, these drugs are cleared from the tissue without interacting with the CYP3A4 and CYP3A5 isoforms of the CYP450 system which is the pathway used by statins and other agents. As a result, ASOs can be used in combination with other cardiovascular therapeutics [39].

In a clinical study done by Jensen et al., increasing doses of Volanesorsen were given to healthy individuals and patients with CVD via subcutaneous injections [43]. Three doses were given in the first week (days 1, 3, and 5) followed by three weekly doses (days 8, 15, and 22). One week after the last dose, a decline in TG levels corresponding to a reduction in ApoCIII levels was observed in a dose-dependent manner. The drug was well tolerated with no side effects in the phase I study [44]. Despite promising data from the phase I study, the Volanesorsen drug was seen to cause reactions at the injection site in the patients versus no such reaction was seen in the placebo group. Interestingly, a significant decrease in platelet counts in two patients from the treatment group led the study to pause and there is an ongoing debate about the safety of this drug and events of thrombocytopenia (low platelets) [44]. Another ASO drug, AKCEA-APOCIII-LRx was assessed in a clinical trial (NCT02900027) for safety, tolerability, and efficacy. AKCEA-APOCIII-LRx was well tolerated with no reactions at injection sites, no deaths, no thrombocytopenia events, and similar efficacy as Volanesorsen but at 15-30-fold lower systemic doses [45]. This drug is currently under phase III trial for clinical validation of its efficacy.

Limitations

ApoCIII plays a key role in thrombin generation through stimulation of monocyte activation using Toll-Like Receptor 2 signaling. The hypercoagulation role of ApoCIII may predispose patients to acute thrombotic events or even cardiovascular complications [31]. However, the use of an ASO inhibitor of ApoCIII also downregulates thrombin generation affecting the coagulation cascade. This was one of the major side effects observed in the Volanesorsen drug trial. There is no conclusion to date regarding the side effect being an on-target effect of reduced ApoCIII activity or an off-target effect of Volanesorsen. ASOs as subcutaneous injections must be administered every 4 weeks due to their degradation in vivo in contrast with the base editing by the clustered regularly interspaced short palindromic repeat (CRISPR)/ CRISPR-associated (Cas) system to provide a long-term efficacy approach [38]. This sets the stage to conduct research into developing a one-time drug to resolve dyslipidemia.

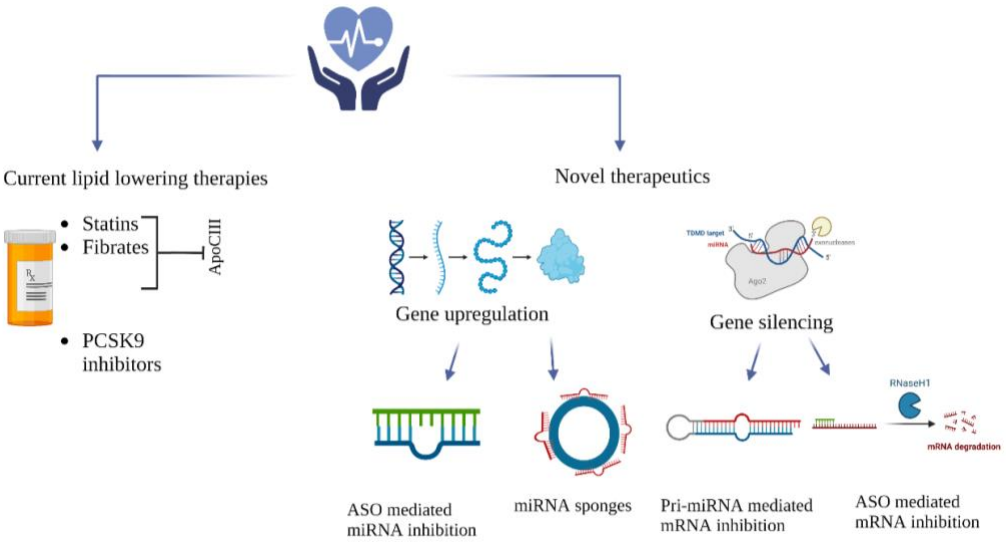

Figure 1. Current versus novel CVD therapeutics (created using https://biorender.com/).

Discussion

MicroRNA regulation of differentially expressed miRNAs in a diseased state and inhibition of the ApoCIII gene in CVD patients can be substantially accomplished by using the same antisense oligonucleotide technology through two different approaches - non-enzymatic and enzymatic. The non-enzymatic approach includes hybridization to endogenous miRNAs preventing them from interacting with their target mRNA or using synthetic miRNA mimics which can inhibit mRNA translation by blocking the initiation sites. The enzymatic approach involves ASO-guided, RNaseH or double-stranded RNase catalyzed degradation of target complementary mRNA in the nucleus or RISC/Argonuate2 catalyzed degradation in the cytoplasm. While target specificity needs to be addressed for miRNA therapeutics, ASOs targeting ApoCIII are efficiently delivered to the liver- the site of lipid metabolism via subcutaneous injection emphasizing the importance of understanding the target pathway to optimize drug delivery [9]. Most of the drugs in human clinical trials are ASOs due to their ability to bind to the serum proteins, slowing renal clearance, whereas siRNAs with hydrated surfaces interact poorly with cell surfaces leading to their excretion [46]. Interestingly, many cell types express surface receptors that enable active uptake of oligonucleotides making them a preferred method for gene regulation in vivo [47].

To address targeted delivery, Sun et al. successfully administered miR-148a - responsive PGC1α (peroxisome-proliferator-activated receptor-γ coactivator-1 alpha) mRNA into exosomes and delivered the exosomes to the target site (adipose tissue) with the help of Ultrasound Targeted Microbubble Destruction (UTMD) [48]. More studies are needed to explore the efficacy of the UTMD method in resolving cardiovascular homeostasis. Furthermore, a study done by Khetarpal et al. showed that in heterozygous carriers of the ApoCIII mutation, there was a lower level of plasma TG than in non-carriers; nevertheless, there was no significant difference in the platelet counts or prevalence of thrombocytopenia [49]. This suggested that the side effect was not a property of ApoCIII inhibition. Off-target effects are common in oligonucleotide-mediated gene silencing which must be minimized by careful use of chemistry to determine a highly specific ASO.

Conclusions

In theory, the use of miRNA therapeutics to resolve disease pathology appears to be promising. However, there is a large gap in the translation of miRNA therapeutics for practical application due to a lack of stable, target-specific delivery methods. The collaboration of technology to engineer exosomes or lipid nanoparticles, and to direct ultrasound-focused delivery of nanoparticles carrying desired miRNA cargo to the target organ has a great potential to be used in clinical therapies including that of cancer. More animal studies specific to CVDs are needed to address the kinetics of clearance, dosage, and side effects. Currently, ASO-mediated gene silencing of the ApoCIII gene seems to be the most feasible RNA therapeutic to address dyslipidemia associated with CVD.

List of Abbreviations Used

AAA: Abdominal aortic aneurysm
amiRNA: artificial microRNAs
ASOs: antisense oligonucleotides
CAARP: currency, relevance, authority, accuracy, and purpose
CAD: coronary artery disease
CAS: CRISPR-associated (Cas) system
CEPT: cholesteryl ester transfer protein
CircRNAs: circular RNAs
CRISPR: clustered regularly interspaced short palindromic repeat
CVD: cardiovascular diseases
ECM: extracellular matrix
eNVs: extracellular nanovesicles
EVs: extracellular vesicles
HDL: high-density lipoproteins
ICAM-1: intercellular adhesion molecule 1
KOBAS: KEGG orthology-based annotation system
LNA: locked nucleic acid
MI: myocardial infarction
miR: microRNA
miRNA: microRNA
NF-κB: nuclear factor kappa B
PCSK9 : proprotein convertase subtilisin/kexin type 9
PGC1α: peroxisome-proliferator-activated receptor-γ coactivator-1 alpha
RISC: RNA-induced silencing complex
siRNA: small interfering RNA
TG: triglyceride
TMTME: too many targets for microRNA effect
UTMD: ultrasound targeted microbubble destruction
VCAM-1: vascular cell adhesion protein 1
VLDL: very-low-density lipoproteins

Conflicts of Interest

The author declare that there were no conflicts of interest.

Ethics Approval and/or Participant Consent

The study did not involve human participants. No research ethics board (REB) approval was needed.

Authors' Contributions

KBP: designed the study, drafted the manuscript, critically appraised, and revised the manuscript, and gave approval for the final version to be published.

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