COMMENTRY

Beyond covid-19: m-rna and its therapeutic use

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ABSTRACT

Heart valve repair and replacement is an invasive surgery which may compromise quality of life for the patients concerned. Therefore, patients who had heart valve surgery need rehabilitation interventions to prevent potential complications, and to promote quality of health. A rehabilitation programme is a medically supervised intervention which can assist patients coping with challenges related to heart surgeries and prevent potential complications. This review was undertaken to identify core components of a cardiac rehabilitation programme which can feasibly be adopted for the rehabilitation of patients who had heart valve surgeries locally. A literature review of articles on best practices regarding the core components of cardiac rehabilitation for patients who underwent heart valve repair or replacement surgery was undertaken. Published international guidelines of best practice for cardiac rehabilitation from 1993 to 2018, available in English language were identified through a search of electronic database and reviewed.

A total of 20 articles on cardiac rehabilitation programme were retrieved. Out of the total, only 8 articles meet the criteria and the data were collected from the 8 articles. The findings indicated that patient assessment, exercise, physical counselling, diet/nutritional counselling, tobacco cessation, mental health, return to work, lipids, hypertension, cardio-protective therapies are essential components for the rehabilitation after heart valve surgeries, to support patients and their families to cope with challenges related to surgeries. These in return improve quality of life for the patients concerned. The core components for the cardiac rehabilitation programmes as highlighted by the international guidelines can be adapted to the cardiac rehabilitation programme in Namibia if tailored to the contextualized needs for the cardiac patients in Namibia.

Key Words: *Covid-19; Sars-Cov-2; Coronavirus; Pandemic; Spironolactone*

INTRODUCTION

Although the COVID-19 pandemic, which began late in 2019, focused attention on using chemically modified mRNA technology to stop the disease from spreading, the technology's implications in the prevention and treatment of other diseases should not be disregarded. Indeed, the origins of this next-generation technique may be traced back over two decades, with a primary focus on cancer treatment [1]. With an Emergency Use Authorization (EUA) granted to Pfizer-Biotech and Moderna COVID-19 vaccines, the FDA gave the first-ever approval of mRNA-based vaccinations in less than a year from the start of the COVID-19 pandemic. The FDA has awarded the first full approval to the Pfizer-Biotech COVID-19 vaccine, which is being marketed under the name COMIRNATY, on August 23, 2021. Many research organizations have already begun working on the production of agents from this class of biologics to control various diseases. These innovative vaccinations have offered proof of concept for the readiness of this strategy in addressing challenging disease conditions. In fact, distinct types of chemically modified mRNA can play prominent roles in a variety of illness situations when used for therapeutic objectives such as genome engineering, immunotherapy, genetic reprogramming, and protein replacement therapies. Because of its high vulnerability to breakdown by extracellular RNases and the difficulties in moving this huge molecule through cellular membranes, using naked mRNA to treat illnesses is problematic, resulting in decreased stability and inadequate mRNA delivery. Various pharmaceutical delivery techniques have been developed to improve the distribution of synthetic mRNAs. The gold standard approach involves forming lipid nanoparticles from negatively charged modified mRNA by electrostatic binding of polymers or cationic lipids [2]. The biodegradable, biocompatible, and therapeutic effect-prolonging

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properties of the modified mRNA-coated lipid nanoparticles were demonstrated. Furthermore, lipid nanoparticles encased in mRNA successfully interact with cell membranes, resulting in facilitated endocytosis and cellular uptake, which can be used as a targeted delivery strategy has been approved. Because of its high sensitivity to destruction by extracellular RNases and the difficulties in moving this huge molecule through cellular membranes, naked mRNA is difficult to use to treat illnesses, resulting in decreased stability and inadequate mRNA delivery. Various pharmaceutical delivery techniques have been developed in order to enable better distribution of synthesized mRNAs. Lipid Nanoparticles (LNPs) produced by electrostatic binding of polymers or cationic lipids with negatively charged modified mRNA are the gold standard approach. The biodegradable, biocompatible, and long-lasting therapeutic impact of the modified mRNA-coated lipid nanoparticles was demonstrated. Modified mRNA has a number of advantages over regular DNA-based delivery methods. The fact that mRNA does not penetrate the nucleus or integrate into the genome of the host is one of the key advantages. Furthermore, mRNA has no risk of mutagenicity, which is a major disadvantage of DNA-based delivery systems. In addition, modified mRNA can effectively use the cell's translation machinery to create therapeutic proteins in a dose-dependent way. Furthermore, the chemically modified mRNA has a higher safety profile because the danger of immunogenicity is reduced due to the structural and nucleotide alterations [3]. Furthermore, synthetic mRNA-based therapy is thought to be less expensive, faster, and easier to make on a big scale. Because of the exceptional. Modified mRNA has been studied for several preventive and therapeutic purposes in various disease states, including chronic diseases, due to its characteristics and qualities. Diabetes, methyl malonic academia, cancer vaccination and immunotherapy, osteoporosis, osteoarthritis, osteointegration, tendinopathies, asthma, cystic fibrosis, Ischemic Heart Disease (IHD), heart failure, myocardial infraction, atherosclerotic restenosis, chronic liver injury, PFIC3 (progressive familial intrahepatic cholestasis type 3), Alpha 1-Antitrypsin (AAT) deficiency.

Modified mRNA has a basic structure that is similar to that of native mRNA. Chemical alterations can be applied to different sections of the mRNA structure to improve its integrity, efficiency, stability, and safety in order to improve translation and/or half-life. For efficient mRNA translation, which occurs through the 5′ cap, a functioning 5′ cap structure is essential. On the other hand, the binding of the 5′ cap to the mRNA decamping enzymes (DCP1, DCP2, or DCPS) regulates mRNA decay. New cap analogues with a 1,2-dithiodiphosphate moiety along a tri- or tetra phosphate bridge were created as mRNA modification reagents in a study. These cap analogues have been demonstrated to have a strong affinity for EIF4E and to be resistant to the SpDcp1/2 decamping complex. Furthermore, the poly(A) tail is found at the end of mRNA and regulates the efficacy and stability of translation [4]. Using recombinant poly(A) polymerase, which helps prolong produced mRNA enzymatically by inserting changed nucleotides into the poly(A) tail, is one way to modify the poly(A) tail. In vitro transcription of mRNAs with poly(A) tail modifications and the insertion of pseudo uridines resulted in improved biological stability, higher translational capabilities, and no immunogenicity, according to Karikó. Additionally, regulatory sequence components known to affect the stability and translation of endogenous mRNA, such as-globin 3′ -UTR sequences, can be added to optimise the 5′ - and 3′ -UTRs regions.

Finally, ORF (coding region) optimization can be achieved by replacing unusual codons with common ones to improve translation efficiency. To improve the safety of mRNA-based treatments, many optimizations may be implemented.

METABOLIC DISEASES

Modified mRNA has been shown in several trials to direct non-endocrine pancreatic cells to make insulin endogenously to treat diabetes. Koblas et al. revealed that by delivering modified mRNA that encodes the transcription factor neurogenin-3 and tiny chemical compounds to reprogram the epigenetic state, pancreatic organoid cells may be encouraged to function as insulin-producing cells. Their findings revealed that the reprogrammed cells kept the usual physiologic activity of pancreatic -cells, as evidenced by insulin, glucosidase, and essential transcription factors expression [5]. When extracellular glucose concentrations were raised, however, the insulin-secretory efficiency was slightly improved. These data suggest that the modified mRNA under investigation can partially modify pancreatic cell insulin production. More research is needed to support the use of chemically modified mRNA as a monotherapy function in DM, especially type 1, by adding distinct or dual genetic material encoding additional proteins to boost the secretory potential of insulin-secreting cells and maintain glucose homeostasis. Human Pancreatic Duct-Derived Cells (HDDCs) were transfected with synthetic modified mRNA expressing essential pancreatic transcription factors (neurogenin3, pancreatic duodenal homeobox 1, and V-Maf musculoaponeurotic fibro sarcoma oncogene homolog A) in another study with a similar goal. In vitro, this transfection caused HDDCs to differentiate into -cells. Within one week, 37% of insulin-positive cells were discovered, according to reports. In response to various stimuli, such as glucose, the HDDC-derived -cells were capable of generating C-peptide and insulin. When HDDC-derived -cells were given to a diabetic mouse model in an in vivo investigation, hyperglycemia was relieved, and insulin was urged to be generated in response to the high blood sugar level. Similarly, induced pluripotent stem cells iPSCs were effectively created using a modified mRNA reprogramming approach, according to another study. When compared to parental fibroblasts, the modified mRNA created iPSCs resulted in a considerable overexpression of pancreatic specific microRNAs, which are known to promote pancreatic -cell proliferation and insulin secretion. These findings support the idea that chemically modified mRNA could be a promising therapeutic method for treating and reversing type 1 diabetes. Angiogenesis and vascularization have long been thought to be a promising way to promote and speed wound healing. Interestingly, vascular endothelial growth factors A (VEGF-A) has been extensively explored for its advantageous properties in gene transfer, with modified mRNA representing a feasible way to overcome several constraints associated with other genetic and reprogramming routines [6]. Using a diabetic wound healing animal model, a group of researchers investigated the effects of delivering a modified mRNA harboring genetic material encoding the Vascular Endothelial Growth Factor A (VEGF-A) protein. This study discovered a dose-dependent improvement in vasodilation, vascularization, and wound bed oxygenation. As a result, there has been an increase in re-epithelialization during the early stages of diabetic wound healing [7].

TYPES OF ONCOLOGY

Chemically modified mRNA has been intensively investigated as a cancer immunotherapy vaccination mechanism, in which both the genetic material and immunological activation of the innate immune system are supplied. Cancer vaccines, unlike prophylactic viral vaccines, are primarily used as a therapeutic method, targeting specific tumor antigens or growth-associated proteins that are commonly produced by malignant cells. These vaccines are frequently coupled with immune modulators such as OX40, CD83, and 4-1BBL to increase their efficiency and potency against cancer cells [8]. Immunostimulant action has been discovered to be important in preventing immune tolerance while targeting cancer self-antigens. After detecting distinct cancer mutations, modified mRNA was used to reprogram natural killer cells and T cells to target specific cancer antigens. Various direct and indirect delivery strategies could be used to effectively transport the mRNA. Ex vivo mRNA injection into dendritic cells can be used for indirect distribution. Different methods of delivery, such as intramuscular, intradermal, intranodal, and intratumoral, could be used to inject mRNA directly. Systemic administration, on the other hand, is avoided to avoid protein aggregation and cellular destruction [9]. RNase enzyme should not degrade the chemically modified mRNA, hence optimized formulations should be used. Many mRNA cancer vaccines for various malignancies have proceeded into phase II and III clinical trials using this technique, which was created several years ago.

MUSCULOSKELETAL PROBLEMS

The WHO in a variety of musculoskeletal illnesses, disease modelling with changed mrna can be beneficial. Bone morphogenetic protein 2 (BMP-2) is one of the most important biomarkers, as it is involved in bone and cartilage growth and development. As a result, mRNA coding for BMP-2 has the potential to be useful in the treatment of a variety of bone-related illnesses. Synthetic mRNA encoding BMP-2, when loaded into Transcript Activated Matrices (TAMs), produced a sustained steady-state protein expression for roughly seven days with a continued residual production for around ten days after transfection, according to two investigations. BMP-2 mRNA expression resulted in osteogenic differentiation and expression of osteogenic markers in a preosteoblast cell line in vitro. Furthermore, bone regeneration was shown in a rat model with a femoral bone lesion. With a more refined mRNA encoding BMP-2, a third research validated similar findings. In vitro and in primary muscle-derived mesenchymal stem cells, this chemically modified mRNA generated a robust production of BMP-2 protein. Furthermore, after transfection with BMP-2 encoded mRNA, angiogenic and osteogenic genes were observed to be increased in stem cells. When compared to the control group, treated animals with BMP-2 mRNA showed improved bone growth and endochondral osteogenesis in a femoral defect rat model. With larger doses, significant new tissue development and vascularization were also observed. Furthermore, BMP-2 mRNA-treated animals had better vascularization in the healing area. These findings show the important function that changed mRNA could play in poor bone repair diseases like osteoporosis, as well as the potential therapeutic applications. The field of osteointegration is another use of chemically modified mRNA. Osteointegration is a crucial step in achieving implant integration with the surrounding bone tissue. In orthopedics, Biocompatible Titanium (Ti) implants have been successfully produced to correct bone deformities. Synthetic mRNA has been researched for the delivery of osteoinductive proteins to increase implant osteointegration due to its potential in encouraging bone healing. Ti implants covered with various biomaterials were developed by a research team to deliver mRNA in a regulated release pattern.

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