NTA2022

2nd International Conference on
Nanotechnology: Theory and Applications,
Cairo, 19 – 21 Dec., 2022

Ref. 024

MicroRNA-199a loaded gold nanoparticles; A promising tool to combat hepatocellular carcinoma

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KEYWORDS

Gold nanoparticles, hepatocellular carcinoma, MET pathway

SHORT SUMMARY

Gold nanoparticles of size 12.5 – 15.5 nm were loaded with miRNA to reach a size of 12.3 – 17.43 nm. Their effect on hepatocellular carcinoma was studied. It was found that miRNA loaded AuNP hold a great potential as a therapeutic agent to combat HCC through inhibition of proliferation and enhancing apoptosis

EXTENDED ABSTRACT

Introduction

MicroRNAs (miRNAs) are small, non-coding RNAs that downregulate the expression of their target genes post-transcriptionally and, in doing so, control a multitude of fundamental biological processes. Recently, pivotal roles of miRNAs in the development and progression of cancer have become widely acknowledged. Extensive studies have proven that the expression profiles of miRNAs are frequently altered in hepatocellular carcinoma (HCC), and miRNAs have been shown to contribute to the development and progression of HCC.

Current therapeutic strategies for HCC still fall short of being safe and effective at eradication of the disease, and therefore, new treatment modalities are warranted. miRNAs have been considered as potential therapeutic targets for HCC. miR-199a has recently emerged as a key player in the pathogenesis of HCC. The downregulation of miR-199a has shown to be a pivotal driver for hepatocellular carcinoma proliferation and survival through downregulation of the MET pathway leading to reduced cellular proliferation as well as downregulation of the matrix metallo-proteinase-9 pathway leading to induction of apoptosis and cell cycle arrest.

Delivery of miRNAs intracellularly poses a challenge since bear miRNA molecules lack the capability for intracellular internalization, therefore, designing nanocarriers for efficient delivery is a must. Inorganic materials, including gold nanoparticles (AuNPs), have been developed as efficient vectors for miRNA delivery. AuNPs are not only inert and biocompatible, but they also can be easily attached to functional groups such as thiol and amino groups present on the ends of functionalized miRNA particles. Additionally, AuNPs can be used as double ended swords, making good advantage of its unique surface plasmonic resonance properties for further destruction of cancer cells using hyperthermia, as well as its inherent fluorescent properties allowing for examination using fluorescent microscopy.

Aim of the work

The present work aims to assess the effects of miR-199a loaded on AuNPs on inhibiting proliferation and enhancing apoptosis in hepatocellular carcinoma cell lines.

Material and Methods

- AuNPs were prepared using a citrate mediated reduction method, and loaded with miR-199a and characterized using HR-TEM, UV spectrophotometer and zeta potential before and after loading.
- Cytotoxicity tests were done using MTT at 3 times intervals 24, 48 and 72 hours to determine the IC_{50}.
- Cellular uptake was evaluated using confocal microscope and TEM.
- Apoptosis and the proliferation were assessed using flow cytometry using Ki-67 and Annexin V.
- Morphological assessment of the cellular changes before and after transfection with miR-199a.

Results

- AuNPs were circular in shape with a size ranging from 10.5-15.3 nm and their size increased to 12.3-17.43 nm after loading with miR-199a.
- The zeta potential was -99 mv before loading miR-199a and -29 mv after loading with miR-199a.
- Cellular uptake was confirmed by confocal microscopy and TEM with both cytoplasmic and intranuclear NPs. Cells incubated for 24 hours with the AuNP-miR-199a showed signs of apoptosis such as cytoplasmic shrinkage, nuclear fragmentation, and formation of apoptotic bodies.
- AuNPs- miR-199a induced apoptosis in HCC cell lines up to 91.5±6.58 % ($p < 0.05$) and reduced proliferation rate to 8.83 ± 3.15 % ($p < 0.05$).

Conclusion

The gold nanoparticles are effective and efficient carriers for MicroRNA where it increases the intracellular delivery into the cytoplasm and nucleus of HCC cell lines.

miR-199a loaded on gold nanoparticle holds a great potential as a therapeutic agent to combat HCC through inhibition of proliferation and enhancing apoptosis.