Paclitaxel Loaded Magnetic Nanoparticle Labeled Mesenchymal Stem Cells as Drug Delivery Vehicle in Cancer Therapy

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ABSTRACT SUMMARY
Compared with traditional molecular based contrast agents or therapeutics drugs, the nanomedicine paradigm enables a highly integrated design that incorporates multiple functions such as cell based targeting, ultra sensitive imaging and therapy. In this scenario, superparamagnetic nanoparticles act as an efficient theranostic tool by simultaneous action as a drug delivery vehicle and also as a contrast agent for magnetic resonance imaging. In addition, targeted delivery of therapeutics at the tumor site without affecting the normal tissues has always remained a challenge. The homing property of mesenchymal stem cells (MSCs), specifically towards the tumor tissues suggests its potential to be used as a delivery vehicle for cancer therapeutics. The objective of our study is to develop therapeutic loaded magnetic nanoparticles (MNPs) and label MSCs with the above MNPs, which will act as a novel therapeutics agent.

INTRODUCTION
The main objective in cancer chemotherapy is to localize the action of the chemotherapeutic agent at the tumor site that will result in killing of cancer cells without any collateral side effects to the healthy cells. With the advent of nanoparticle mediated drug delivery, targeted drug delivery has become possible but with limitations imposed by different physiological barriers. Thus the primary objective of current cancer therapeutic invention is to overcome the critical physiological barriers posed by the systemic defense, to understand the abnormal tumor structure for high tumor targeting efficiency and for homogenous intra tumoral drug distribution. In this regard, cell based therapy has brought some hope to achieve tumor targeted drug delivery.

EXPERIMENTAL METHODS
The MNPs are synthesized by co-precipitation method. Paclitaxel loaded MNPs were formulated by adding 10 mg paclitaxel to 100 mg MNPs with overnight stirring. The detailed physicochemical characterization of the formulated pac-MNPs was done by studying the hydrodynamic size and zeta potential by dynamic light scattering, atomic force microscope. The drug entrapment efficiency was calculated by RP-HPLC. The mesenchymal stem cells were labeled by pac-MNPs that can be visible by transmission electron microscopy. The effect of paclitaxel on the MSCs was studied by alamar blue experiment in a time dependent manner. The release kinetics of paclitaxel from the pac-MNPs labeled MSCs was checked by RP-HPLC. The effect of pac in a coculture of MSCs and MCF-7 cells (breast cancer cells) was studied by alamar blue experiment. The migration efficiency of pac-MNPs labeled MSCs towards MCF-7 cells was studied in a trans-well migration experiment and also the toxicity was assessed by alamar blue experiment.

RESULTS AND DISCUSSION
Labeling the mesenchymal stem cells with magnetic nanoparticles is a new avenue in the field of regenerative medicine and theranostics related to cancer therapy and diagnosis.
The formulated pac-MNPs have hydrodynamic size of ~ 160 nm and high positive zeta potential of 23 mV. Atomic force microscopy suggests its smooth topology (Figure 1). Quantification of paclitaxel entrapped within the MNPs was done by HPLC was ~ 85%.

Before labeling the MSCs, the effect of paclitaxel on the MSCs has to be checked. The alamar blue experiment results suggest that paclitaxel doesn’t kill the MSCs which can be seen in 24 h result. But, the 48 h and 72 h results suggest that there is inhibition in proliferation of the MSCs which may be due to action of paclitaxel on mitotic spindles (Figure 2). This suggests that the pac-MNPs labeled MSCs will not proliferate but will survive to show other stem cell properties.

After checking the cytotoxic effect of paclitaxel on MSCs, next we have checked the release of drug from pac-MNPs labeled MSCs.

The HPLC quantification results suggest that there is gradual efflux of paclitaxel from pac-MNPs labeled MSCs to outside medium (Figure 3). This suggests that the pac-MNPs labeled MSCs will act as a drug delivering MNPs labeled MSCs help to induce cell death of the cancer cells. The results suggest that with increasing concentration and time period there paclitaxel affect the cell growth (Figure 4). When correlated with the results in figure 1, it can be confirmed that paclitaxel kills the MCF-7 cells. Also, with increasing number of labeled cells, cytotoxic effect towards MCF-7 cells has increased (Figure 5).

Besides, the trans-well migration experiment suggest that the labeled cells migrate towards the cancer cells and help in cancer cell death (Figure 6).

CONCLUSION

The present study demonstrates development of a cell based therapeutic system that will act both for diagnosis, tracking and therapeutic agent. Paclitaxel-MNPs labeled MSCs shows superior advantages tumor directed drug delivery. The combination of “stem cell targeting” and “controlled drug delivery” has the capacity to selectively target the tumor cells without the side effects towards the healthy tissues. This promising and effective strategy will provide a strategy for effective cancer therapy in future.

REFERENCES


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