Targeted nanodrug delivery systems for the treatment of Tuberculosis

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Introduction

South Africa currently has the highest incidence of TB per 100 000 (358 per 100 000) people in the world. In 2007 alone 112 000 people died of TB in South Africa, of which 94 000 (72%) were co-infected with HIV (1). Although TB treatments exist, poor patient treatment compliance and drug resistance pose a great challenge to TB treatment programs worldwide. To improve the current inadequate therapeutic management of TB, a polymeric anti-TB nanodrug delivery system for anti-TB drugs was developed that may enable entry, targeting, sustained release over long periods and uptake of the antibiotics in the cells, hence reducing the dose frequency and simultaneously improving patient compliance.

The aim was to prepare functionalised polymeric nano drug delivery vehicles to target TB infected macrophages. Successful nano encapsulation of anti-TB drugs and a targeting agent, mycobiocids (MA) was achieved. MA (a lipid molecule on the cell wall of M.tb) was explored due to its cholesterol properties (2) that could attract it to the infected macrophages/foam cells. The nanoparticles were characterized and subjected to in vitro uptake in THP and U937 cells to determine their uptake and localization. Cytotoxicity in different cell lines was also analysed. In another approach targeting was attempted by attaching nucleic acid aptamers (3) onto the surface of drug-carrying PLGA nanoparticles. The aptamers were prepared via the SELEX process (4), specifically against the mannose receptor (MR), which is significantly over-expressed during the activation of the macrophages in the presence of M.tb.

Experimental and Results

Targeting ligand: Mycobiocids

Mycobiocids (MA) make up the major part of the cell envelope of Mycobacterium tuberculosis. MA was shown to assume a fine structure-dependent cholesterol nature that attracts cholesterol (2, 6) and converts macrophages into foam cells (5). It is actively pumped into the extracellular matrix of M.tb, biofilms during the drug resistant persistent phase (7), where it may possibly be targeted as a cholesterol rich zone.

THP-1 and U937 monocyte-macrophage like cell lines were used to determine whether the labeled MA nanoparticles would be taken up by the cells. The data presented in Fig 1 illustrate that labeled MA nanoparticles were taken up into the macrophage cells, demonstrating that MA-nanoparticles may serve as a suitable carrier for anti-TB drugs.

Discussion and conclusion

MA as targeting ligand derives from its cholesterol attracting property. MA NP was taken up into macrophages in vitro, possibly localizing in the cytoplasm. In vitro drug testing via BACTEC indicated that the INH was released from the NP, but that the MA does not show advantage in the early mycobacterial replication.

Aptamers against the mannose receptor protein were made and coupled onto the surface of the PLGA nanoparticles. In vitro drug testing and confocal imaging are underway.

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References