Title:	PULMONARY DELIVERY OF ANTIMICROBIAL PEPTIDES (AMP) USING POROUS NANOPARTICLES AGGREGATES (PNAPs) FOR TARGETING ALVEOLAR MACROPHAGES AGAINST PULMONARY TUBERCULOSIS
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Abstract:	The prospective to progress pulmonary tuberculosis (TB) therapy outcomes with adjunctive therapies requires investigation. The objective of the present work was aimed to investigate the role of exogenous delivery of antimicrobial peptides (AMPs) using inhalable formulations against pulmonary tuberculosis as an adjunct therapy along with contemporary anti-TB treatment with increased activity and patient compliance. Several AMPs have antimycobacterial potential which provides them as appropriate therapeutics but due to poor pharmacokinetic profile, salt sensitivity, presence of proteases in the biological system makes them highly unstable with very diminutive half-life hence, is exigent to deliver as such in biological system in a sustained and controlled way for therapeutic rationale. The study was performed to target lungs locally using various Inhalable biodegradable formulations encapsulating substantial amount of AMPs shows raised area to release AMPs locally (alveolar macrophages) at beneficial level over extended period of time at site of infection for the treatment of pulmonary tuberculosis (TB). Double emulsion method was used to prepare porous microspheres and spray freeze drying was used to develop inhalable Porous nanoparticles aggregate particles (PNAPs) containing individual AMPs alone) for pulmonary delivery. All the developed formulations had optimized aerodynamic properties to deposit into lungs with cascade impaction. MIAP, UB2, Aurin, K4, HHC- 10, Indolicidin and IDR-1018 were synthesized using solid phase peptide synthesis and individually incorporated in various delivery systems with encapsulation efficiencies of ~50% to obtain particles (MP) yields of >60%. The Mass Median Aerodynamic Diameter (MMAD) of the MP was 2.2-2.4 µm within geometric standard deviations (GSD) of ≤ 0.1 µm. MP were phagocytosed by RAW 264.7 macrophages in culture and significantly (P<0.05) dose-dependent killing of intracellular Mtb by formulation compared to equivalent amounts of drugs in solution was observed on estimation of colony forming units (CFU). Cytotoxicity of MP towards macrophages was lower than that of dissolved drugs. The in-vivo efficacy of individual AMPs and with anti-TB combinations Isoniazid was evaluated in Swiss mice infected with virulent (H37Rv) mycobacterium after 6 weeks (5days/week) multiple dose pulmonary delivery which was further compared with standard oral Anti-TB therapy. The results reveals the formulations containing indolicidin and IDR-1018 exerts significant antimycobaterial activity against virulent Mycobacterium tuberculosis (H37Rv) in vivo. AMPs releasing inhalable microparticles demonstrated enhanced bactericidal efficacy and normalized lung and spleen morphology. Attempt was made to elucidate the cellular and molecular vimechanism by which AMP kills the bacteria. Our results suggest that different exogenous AMPs exerts multiple mechanisms to enhance bacterial killing inside inected macrophages like phagolysosomal fusion, membrane permeabilization also enhance apoptosis in infected macrophages. It is concluded that developed inhalable formulations containing AMPs can were formulated best depending upon their aerodynamic capacity, encapsulation efficiency in vitro and in vivo efficacy. These results display the advantage of pulmonary delivering of AMPs via formulation for antituberculosis application an adjunct therapy along with standard DOTS therapy.
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