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Membrane affinity of antituberculotic drug conjugate using lipid monolayer containing mycolic acid

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ABSTRACT

Surface behaviour of mixed monolayers of DPPC and mycolic acid as a specific membrane component of *Mycobacterium tuberculosis* were studied by Langmuir-balance technique. Additivity analysis of the surface pressure–area isotherms showed that mixed layers are expanded at higher temperature (36 °C) while negative excess surface areas were obtained depending on the composition at lower temperature (24 °C). Strong condensation and aggregated structure of the mixed layer was revealed by AFM.

Isoniazid (INH) which is an effective bactericidal synthetic therapeutic agent for the treatment of tuberculosis was conjugated with a tuftsin derivative (TKPKG) and a lipophilic molecule (palmitic acid) to enhance its specific delivery and cellular uptake. Membrane affinity of the lipopeptide conjugate pal-T_5-$(INH)_2$ was estimated from penetration experiments using model lipid monolayers. Degree of penetration was higher into mycolic acid containing monolayers than to phospholipon. The lipopeptide conjugate pal-T_5-$(INH)_2$ presented the highest membrane affinity to DPPC:MA layer at lower temperature. Temperature dependent organization of the mixed film was in accordance with the degree of penetration indicating the importance of structural characteristics in molecular interaction between drug and membrane components.

1. Introduction

Tuberculosis is an infectious disease and one of the leading causes of death in the world. The pathogen responsible for the disease is *Mycobacterium tuberculosis* (*Mtb*) causes 8 million infections and nearly two million deaths every year [1]. Among the difficulties of the therapy for tuberculosis are the long duration of treatment, the drug toxicity which is increasing with the dose, and heavy side effects, furthermore the emergence of drug resistance. The aim is to shorten the duration of treatment hence reducing harmful side effects by improved transport to the target cells.

The chemotherapy of tuberculosis and development of new antitubercular drugs need the knowledge of structural and physicochemical properties of the cell envelope of *Mtb* [2]. Various strategies have been proposed to inhibit the duplication of bacteria. Isoniazid which has been used as a front line drug for treatment against tuberculosis for decades inhibits the synthesis of mycolic acids. Since mycolic acids are major and specific constituents of the cell envelope, the inhibition of their biosynthesis directly disturbs the duplication of cells.

The cell envelope of *Mtb* is roughly described as layer of plasma membrane, peptidoglycan, arabinolactan and the most outer layer containing mycolic acids. Almost 40% of the mycobacterial cell wall lipid is mycolic acid [3]. Mycolic acids are high molecular weight α-alkyl-β-hydroxy fatty acids having asymmetrical and folded hydrocarbon chains. The exceptionally long hydrocarbon chains referred to as the mero group are associated with the short chain of C22–C25 hydrocarbons. The folding and unfolding of mycolic acid chains can influence their roles as permeability barriers for drugs [4] and resulting in hydrophobic surfaces [5,6].

Conjugation of drug molecules with peptide carrier or other moieties is a promising approach to increase the efficacy of widely used drugs by enhancing their transport to the target cells [7,8]. Peptide conjugates allow the enhanced transport by specific receptor mediated endocytosis. The conjugation on the other hand, might alter the hydrophobicity of the molecule and the emergence of amphipathic character is expected to contribute to the increased membrane affinity. Successful homing of a drug to the target cells or organisms (such as bacteria) depends on the design of the carrier molecule. In a typical drug targeting sequel, the carrier-drug unit would preserve its integrity, avoid influencing the surroundings, penetrate interposing membranes and associate with the target before the drug is released [9,10]. Isoniazid (INH) is one of the most effective bactericidal synthetic therapeutic agents for the treatment

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