Membrane affinity of antituberculotic drug candidates

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The treatment of the chronic inflammatory caused by Mycobacterium tuberculosis (Mtb) requires prolonged chemotherapy often associated with unwanted side effects and developing resistant bacterium strains. Therefore improving the efficiency of the present antimicrobial agents e.g. isoniazide (INH) through targeted cellular uptake is desirable. Conjugation of INH with a peptide and other amphiphilic/hydrophobic moiety was designed and the hydrophobic properties, membrane affinity and antimicrobial activity of the INH-conjugates were characterized. On the other hand introduction of new in silico identified drug candidates which are expected to be specific inhibitor of dUTPase a vital enzyme of Mtb presents a novel approach in the combat with the disease. A great number of possible specific inhibitor of dUTPase was identified by simulation methods [1].

Drugs have to be transported through several membranes to reach the infected target cell, therefore the molecular interaction of the drug with lipid membranes was studied in monolayer model systems. Ability and tendency of penetration and incorporation of the drug or drug-conjugate molecules into the lipid Langmuir monolayer as well as the rate of drug penetration were determined tensiometrically [2]. Mycolic acid as an essential component of Mycobacterium membrane was incorporated in the lipid monolayer to get an improved model. The lipid monolayers, containing the penetrated drugs were transferred to a solid support using Langmuir-Blodgett (LB) technique and characterized by atomic force microscopy (AFM). Correlation was found between the degree of penetration and the characteristic changes in the structure of the lipid films (layer thickness, surface roughness).

Since membrane affinity can be considered as a necessary condition for effective drug transport to the targeted cell, the above studies present a high through put technique in the selection of great number of identified and synthesized drug candidates.


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