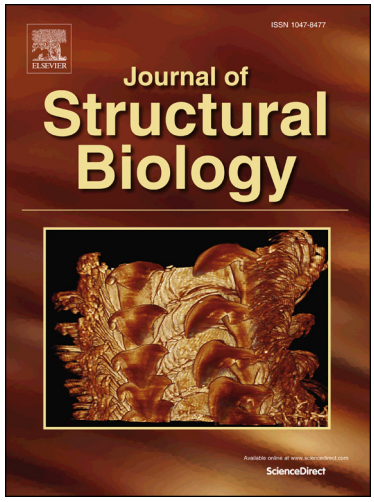

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Human Skin Barrier Structure and Function Analyzed by Cryo-EM and Molecular Dynamics Simulation

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Abstract

In the present study we have analyzed the molecular structure and function of the human skin's permeability barrier using molecular dynamics simulation validated against cryo-electron microscopy data from near native skin.

The skin's barrier capacity is located to an intercellular lipid structure embedding the cells of the superficial most layer of skin — the stratum corneum. According to the *splayed bilayer model* (Iwai et al., 2012) the lipid structure is organized as stacked bilayers of ceramides in a splayed chain conformation with cholesterol associated with the ceramide sphingoid moiety and free fatty acids associated with the ceramide fatty acid moiety. However, knowledge about the lipid structure's detailed molecular organization, and the roles of its different lipid constituents, remains circumstantial.

Starting from a molecular dynamics model based on the *splayed bilayer model*, we have, by stepwise structural and compositional modifications, arrived at a thermodynamically stable molecular dynamics model expressing simulated electron microscopy patterns matching original cryo-electron microscopy patterns from skin extremely closely. Strikingly, the closer the individual molecular dynamics models' lipid composition was to that reported in human stratum corneum, the better was the match between the models' simulated electron microscopy patterns and the original cryo-electron microscopy patterns. Moreover, the closest-matching model's calculated water permeability and thermotropic behaviour were found compatible with that of human skin.

The new model may facilitate more advanced physics-based skin permeability predictions of drugs and toxicants. The proposed procedure for molecular dynamics based analysis of cellular cryo-electron microscopy data might be applied to other biomolecular systems.

Keywords: stratum corneum, skin permeation, cryo-em, molecular dynamics simulation, lipids

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