Interaction of the N-terminus region of Human Dihydroorotate Dehydrogenase (HsDHODH) with Langmuir monolayers

Vicente, E. F.¹; Piccoli, J. P.¹; Costa-Filho, A. J.²; Nobre, T. M.³; Cilli, E. M.¹

¹UNESP, Univ Estadual Paulista – IQ – Araraquara, SP; ²USP - Universidade de São Paulo – FFCLRP – Ribeirão Preto, SP, Brazil, ³Instituto de Física de São Carlos, USP, São Carlos

Dihydroorotate dehydrogenase is an enzyme that plays a key role in “de novo” pyrimidine biosynthesis and catalyzes the oxidation of dihydroorotate to orotate. HsDHODH has a monomeric structure and is associated with the membrane through its N-terminal extension. Thus, understanding in details how the enzyme interacts with the membrane could make a selective target for antiproliferative, antiparasitic, anti-inflammatory and immunosuppressive drugs. In this study, we synthesized the peptide Ac-GDERFYAEHLMTLQGLLDPEAHRLAVRFTSLG-NH₂, corresponding to HsDHODH N-terminus region. As a membrane model, we employed the Langmuir monolayer technique. The adsorption kinetics for the peptide at different concentrations was first evaluated at the bare interface. In DPPC monolayers, the pronounced induction time for the concentration of 50 nmol L⁻¹ suggests that there is an initial step involving the dissociation of peptide molecules for further adsorption at the interface. After adsorption kinetics, the mixed monolayer was compressed, and a plateau is observed at high surface pressure values (25-30 mN m⁻¹), which is also the lipid packing correspondent to the biomembrane. This behavior can be related to some changes in peptide secondary structure, and probably occur to better accommodate the molecule at the interface during the compression. We extended our results to other lipids such as cardiolipin and DPPE, which are major components of mitochondrial membrane. Our results indicated that the fluidity and or the charge of the membrane are important parameters for the adsorption of the peptide. These results are the first evidence of such peptide interaction with membrane, and it may be useful for understanding the mechanism of protein action at the molecular level.

Word Keys: dihydroorotate dehydrogenase, Langmuir monolayers, peptides, SPPS.
Supported by: FAPESP, CNPq, FUNDUNESP and CAPES.