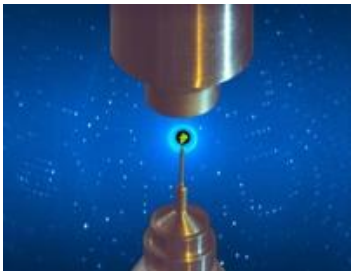

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New insights into the interaction of Class II dihydroorotate dehydrogenases with ubiquinone in lipid bilayers as a function of lipid composition

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The fourth enzymatic reaction in the de novo pyrimidine biosynthesis, the oxidation of dihydroorotate to orotate, is catalyzed by dihydroorotate dehydrogenase (DHODH). Enzymes belonging to the DHODH Class II are membrane-bound proteins that use ubiquinone as their electron acceptor. We designed this study to understand the interaction of an N-terminally truncated version of human DHODH (HsΔ29DHODH), a target for anti-inflammatory drugs, and wild-type bacterial DHODH from Escherichia coli (EcDHODH), with ubiquinone (Q10) in supported lipid membranes using neutron reflectometry (NR). NR allowed us to determine in situ, under solution conditions, how the enzymes bind to lipid membranes and to resolve the location of the Q10. We can show that EcDHODH binds more efficiently to simple bilayers consisting of POPC and TOCL than HsΔ29DHODH. Q10 is exclusively located at the center of all the lipid bilayers investigated, including more complex lipid mixtures mimicking either bacterial or mitochondrial membranes. Incorporation of Q10 into lipid bilayers also increases the efficiency of DHODH binding to the lipid bilayers, as shown by increased enzyme retention upon rinsing. We therefore show that the interaction between the enzymes located at the bilayer-water interface and the membrane is mediated by Q10. Our results highlight the importance of Q10 as well as lipid composition on enzyme binding and enzyme retention.

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