Bilayers at the ILL

Contribution ID: **51** Type: **Poster**

Interaction between human dihydroorotate dehydrogenase and coenzyme Q10 in model lipid bilayers

Wednesday, 11 December 2019 18:36 (1 minute)

In humans, dihydroorotate dehydrogenase (DHODH) is an flavoprotein found in the inner mitochondrial membrane (IMM). DHODH catalyzes the oxidation of dihydroorotic acid with the concomitant reduction of ubiquinone Q10 (coenzyme Q10), thus acting as a link between the *de novo* pyrimidine biosynthesis and the mitochondrial respiratory chain. DHODH is a well validated target for immunosuppressive and antiproliferative compounds that act as inhibitors of the enzyme[1, 2]. Furthermore, mutations in human DHODH have been identified as the cause of Miller syndrome, a rare autosomal recessive disorder resulting in numerous abnormalities of the head, face and limbs [3]. Despite the abundance of crystal structures for DHODH, the mechanisms by which the enzyme interacts with its lipophilic cosubstrate, ubiquinone Q10, are not well understood. We have investigated the interaction between an N-terminally truncated version of human DHODH (lacking the transmembrane domain) and coenzyme Q10 by means of neutron reflectometry (NR) and Quartz Crystal Microbalance with Dissipation Monitoring (QCM-D) under physiologically relevant conditions, using supported lipid bilayers mimicking the composition and structure of the IMM. Our results indicate that DHODH displays higher affinity towards bilayers that incorporate tetraoleoyl cardiolipin (TOCL) compared to bilayers consisting only of phosphatidylcholine (POPC). However, the NR data indicates that the binding between the truncated DHODH and the lipid bilayers studied is weak and reversible, suggesting that the presence of the transmembrane domain might be a prerequisite for stable interaction. We have obtained similar results with bacterial DHODH (originating from *E. coli*), which naturally lacks transmembrane domains.

1. Knecht, W., et al., *Eur J Biochem*, 240, **1996**, p. 292-301.
2. Loffler, M., et al., *Trends Mol Med*, 11, **2005**, p. 430-437.
3. Ng, S.B., et al., *Nat Genet*, 42, **2010**, p. 30-35.

Primary author: OROZCO RODRIGUEZ, Juan Manuel (Lund University)

Co-authors: KRUPINSKA, Ewa (Lund University); FRAGNETO, Giovanna; WACKLIN, Hanna; KNECHT, Wolfgang (Lund University)

Presenter: OROZCO RODRIGUEZ, Juan Manuel (Lund University)

Session Classification: Wine & cheese poster session