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"MECHANISTIC DETECTIVE WORK; THE IMPACT OF A SINGLE PATHOGENIC GENE MUTATION ON THE COMPLEX REACTION PATHWAY OF THE ENCODED PROTEIN"

November 8th, 2019 ~ 11:30AM
Life Science Center II, Room 130

Abstract: The 2-oxoadipate (OA) dehydrogenase complex (OADHc) is a novel multienzyme complex functioning in L-lysine metabolism. A heterozygous missense mutation [c.2185G>A (p. G729R)] has been identified in the DHTKD1 encoding 2-oxoadipate dehydrogenase (E1a, a thiamin diphosphate enzyme) and was linked to pathogenesis of alpha-aminoadipic and alpha-oxoadipic aciduria metabolic disorder. The G729R E1a when assembled to OADHc with the dihydrolipoamide succinyltransferase (E2o) and E3 components of the Krebs cycle 2-oxoglutarate dehydrogenase complex displayed 50-fold decrease in catalytic efficiency for NADH production prompting our multipronged determination of the functional and structural consequences of its origins. While the G729R E1a substitution did not affect reactions associated solely with E1a, production of glutaryl-CoenzymeA by E2o was significantly reduced. Buttressed by chemical cross-linking and HD-exchange mass spectrometric experiments, our studies provide a molecular explanation of the c.2185G>A DHTKD1 pathogenic mutation that causes lysine metabolic disorder: it affects E1a-E2o assembly and substrate channeling in OADHc.

FALL 2019 CHEMISTRY SEMINAR SERIES

HOST: DR. FRIEDER JAEKLE

COFFEE SOCIAL 11:00 AM OLSON HALL, 338

ALL THOSE INTERESTED ARE WELCOME TO ATTEND

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DEPARTMENT OF CHEMISTRY

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