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New flexibility/fold/interactions in the Pyruvate Dehydrogenase complex assembly

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The pyruvate dehydrogenase multienzyme complex (PDHc), is a large, macromolecular machine that converts the product of glycolysis, pyruvate, to acetyl-coenzyme A, with the overall PDHc reaction functioning as a control point in carbohydrate metabolism. Altered levels of PDHc are associated with neurological diseases including Alzheimers and Parkinsons, and because of its role in sugar metabolism, its regulatory mechanisms are targets for controlling type 2 diabetes. Inhibition of PDHc's tissue specific, regulatory kinases increase mitochondrial levels of reactive oxygen species leading to cellular apoptosis and inhibition of tumor growth, suggesting a potential for treating cancer. Two major types of complexes are found: ~4.5 megadalton, octahedral complexes containing 60 enzymatic subunits and having a cubic core; and ~9 megadalton, icosahedral complexes containing ~120 enzymatic subunits and having a dodecahedral core. Multiple copies of at least 3 key enzymatic components, E1, E2 and E3 are always present, while the larger complexes may also contain regulatory phosphatases, kinases, and non-enzymatic, E2-like proteins. The assemblies and unusual substrate channeling mechanism employed by the complexes are fascinating, as intermediates are transferred between active sites by a long, highly flexible, "swinging arm" hand-delivery system employing lipoyl domains rather than by simple diffusion. We have crystallographically analyzed the enzymatic components of PDHc from E. coli, as well as some of their binary sub-complexes. We found that: key E1-E2 interactions stabilizing the overall assembly differ substantially (displaced by over 100 angstroms!) for complexes containing homodimeric vs heterotetrameric E1 components; that the conformation of parts of homodimeric E1's is dramatically stabilized in the presence of its E2 binding partner and reveals a new fold; and that models for octahedral PDHc complexes based on icosahedral complexes are likely to be incorrect.

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