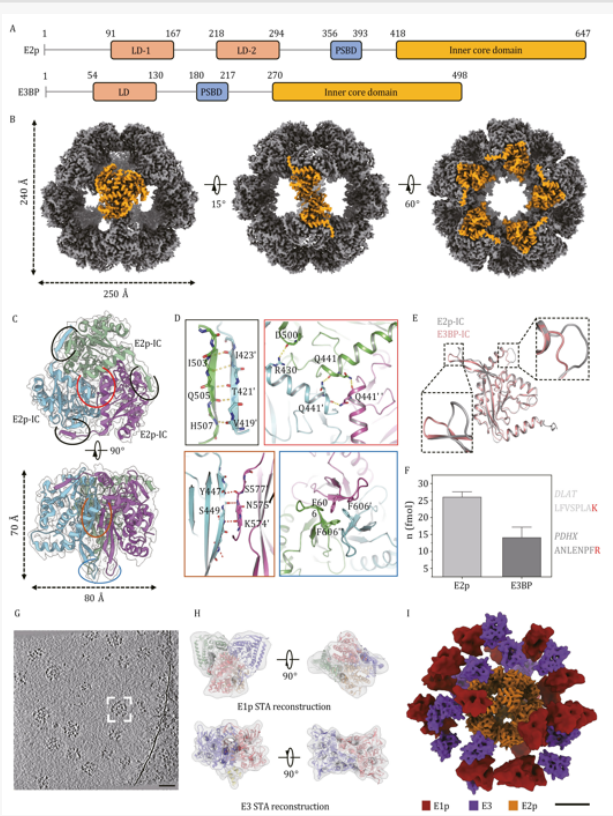
A flexible powerhouse: Researchers unveil the dynamic blueprint of a key metabolic enzyme

GA, UNITED STATES, May 30, 2025 /EINPresswire.com/ -- In a landmark discovery, researchers have unveiled the highly dynamic and adaptable architecture of the mammalian pyruvate dehydrogenase complex (PDHc)—a central enzyme hub that fuels cellular energy production. Leveraging state-of-the-art cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryo-ET), the research team captured the complex in action, revealing a surprising degree of structural flexibility that defies long-standing models. This breakthrough provides critical insights into how PDHc maximizes catalytic efficiency, with significant implications for metabolic disease research.



Structural characterization of Sus scrofa PDHc core and overall landscape of integrated complex. (A) Schematic representation of Sus scrofa E2p and E3BP organization, wherein each structural domain is indicated. Linker regions connecting these domains are

As a gatekeeper between glycolysis and the tricarboxylic acid cycle, pyruvate dehydrogenase complex (PDHc) plays a pivotal role in converting pyruvate into acetyl-CoA. Despite its essential metabolic function, the native architecture of PDHc has remained poorly understood due to its large size and complex organization. Early models proposed a highly ordered structure, yet the precise arrangement and behavior of its peripheral subunits remained a mystery. This structural ambiguity has hindered efforts to decode PDHc-linked disorders, including lactic acidosis and neurological deficits, underscoring the urgent need for high-resolution, in situ visualization.

Published on August 24, 2024, in Protein & Cell, this letter-style study by researchers from Tsinghua University, Shenzhen University, and King Abdullah University of Science and Technology (KAUST), etc. employed cutting-edge cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryo-ET) techniques to visualize PDHc extracted from porcine heart tissue.

The team achieved near-atomic resolution (3.66 Å) of the inner core and captured the elusive dynamics of peripheral enzymes E1p and E3, shedding new light on PDHc's structural organization and functional logic.

The team found that PDHc's core forms a dodecahedral scaffold built from 60 inner core domains, confirming the long-debated "40:20" stoichiometry of E2p to E3BP subunits through quantitative isotopic mass spectrometry. Cryo-ET exposed an unexpected level of peripheral flexibility: E1p and E3 subunits showed no fixed positions but instead formed a dynamic, irregular cloud around the core, breaking with the traditional image of a rigid, symmetrical shell. On average, 21 E1p and 13 E3 subunits were observed per complex, with spatial distributions following a Gaussian profile. Intriguingly, the study revealed novel interaction modes between E1p and E2p's lipoyl domains, suggesting a hidden layer of regulation that may fine-tune the complex's activity under shifting metabolic conditions.

Dr. Sai Li, one of the co-corresponding authors, said: This study overturns decades of structural assumptions. We now understand that PDHc's apparent disorder is, in fact, a design feature—allowing it to rapidly adjust to metabolic demands. This flexible architecture may be the key to its efficiency, and a critical factor in disease pathology when the system breaks down.

These findings could catalyze new therapeutic strategies for PDHc-related diseases, such as inherited metabolic syndromes and mitochondrial dysfunction. By pinpointing the flexible interaction sites within PDHc, researchers can begin to design molecules that modulate its function with precision. Furthermore, the integrative imaging approach showcased in this study sets a new standard for capturing the native states of large, dynamic protein assemblies—opening new frontiers in structural biology, metabolic engineering, and drug discovery.

References

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