Phosphorylation-driven epichaperome assembly is a regulator of cellular adaptability and proliferation

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Abstract

The intricate network of protein-chaperone interactions is crucial for maintaining cellular function. Recent discoveries have unveiled the existence of specialized chaperone assemblies, known as epichaperomes, which serve as scaffolding platforms that orchestrate the reconfiguration of protein-protein interaction networks, thereby enhancing cellular adaptability and proliferation. This study explores the structural and regulatory aspects of epichaperomes, with a particular focus on the role of post-translational modifications (PTMs) in their formation and function. A key finding is the identification of specific PTMs on HSP90, particularly at residues Ser226 and Ser255 within an intrinsically disordered region, as critical determinants of epichaperome assembly. Our data demonstrate that phosphorylation of these serine residues enhances HSP90's interactions with other chaperones and co-chaperones, creating a microenvironment conducive to epichaperome formation. Moreover, we establish a direct link between epichaperome function and cellular physiology, particularly in contexts where robust proliferation and adaptive behavior are essential, such as in cancer and pluripotent stem cell maintenance. In addition, we have developed a strategy to purify and separate ESC HSP90 oligomeric complexes in native states for MS-based proteomics characterization. Our results show the high heterogeneity of stable HSP90 multi-subunit complexes, corroborating its role in the function of diverse proteins and protein assemblies. Furthermore, our data elucidate novel insights on the relationship between the posttranslational modifications and chaperone, co-chaperone composition in these complexes.

Biography

Dr. Feixia Chu is currently a Professor of Biochemistry at the University of New Hampshire. She got her Ph.D. in Chemistry and Chemical Biology with Professor Al Burlingame at the University of California, San Francisco (UCSF), and postdoctoral training in chromatin biology with Professor Barbara Panning at UCSF. Dr. Chu is interested in developing and applying sophisticated mass spectrometric techniques to address complex biological questions, with an emphasis on the nature and function of posttranslational modifications and macromolecular recognitions in complex cellular processes. As PI or co-investigator, her group has elucidated spatial organization of several protein complexes that are central to proteome homeostasis, viral dsRNA recognition, unfolded protein response, vision signal transduction, and transcription elongation. In addition, they have identified key regulatory proteins and posttranslational modifications that modulate chromatin modifier function, gene cluster localization, cAMP signaling pathway in neuronal cilia, transcription regulation, and cell epigenetic state. Strong undergraduate participation is another characteristic of her research program, with several discoveries described in peer-reviewed publications. Dr. Chu has also served on numerous NIH study sections and NSF review panels, as well as the faculty mentor of the UNH student

chapter for the American Society of Biochemistry and Molecular Biology (2014-present).