Amgen Seminar Series in Chemical Engineering

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Optimal Methods and Mass Spectrometry-Based Proteomics for the Characterization of Highly-Modified Protein Systems

By

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The grand problem in biology is to understand how complex and integrated molecular mechanisms govern overall organism function. It has become increasingly recognized that multi-site post-translational modifications (PTMs) of specific proteins modulate their activity, cellular location, and corresponding macromolecular interactions. Many studies support the hypothesis that specific combinations of PTMs on a single protein actually encode for distinct functional states. Examples of such protein systems which are believed to function on the basis of some sort of "PTM code" are histones, microtubules, and several transcription factors, including p53. However, the biological connotations of these combinatorial post-translational modifications remain to be elucidated due to previous limitations in high-throughput separation and detection technologies for hypermodified protein mixtures.

In this work, I will present Bottom Up and Middle Down liquid chromatography tandem mass spectrometry (LC-MS/MS) analytical and computational platforms for identifying and quantifying complex mixtures of highly-modified proteins. Particular emphasis will be on the analysis of histone proteins, whose combinatorial PTMs have been shown to be highly correlated with the formation of euchromatin (i.e., open and transcriptionally active chromatin) and heterochromatin (i.e., compact and transcriptionally repressed chromatin). The potential of this novel high-throughput technology for probing important biological questions regarding the functional implications of hypermodified protein systems will also be discussed.

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