



SEMINARIO

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***An integrative structural biology approach to understand
functional mechanisms in biological complexes***

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Abstract

After >60 years of structural biology, the complexity of both the molecules we study and the questions we pose has increased enormously. Nowadays, we aim to achieve complete spatial/temporal characterization of large molecular complexes during their function, as well as understand the functional mechanisms of disorder and the role of conformational dynamics. In this context, the direction of travel for structural biology is towards integrative methods, where complementarities across cutting-edge technologies are leveraged to address more challenging systems and to understand functional mechanisms in greater depth.

Magnetic resonance makes vital contributions across physical, biological and medical fields, due to its unique ability to study molecules in both the spatial and temporal dimensions, reveal minorly-populated conformations and cope with structural disorder. Furthermore, methyl TROSY and ^{15}N , ^{13}C -direct-detection experiments allow molecular species as large as 1 MDa to be interrogated by solution NMR.

In our laboratory, we use and develop integrative structural biology approaches that employ NMR together with complementary methods to understand the functional mechanism of high-molecular-weight complexes with enzymatic activity. Integrative structural biology in solution is particularly relevant for enzymes that contain disordered parts or for transiently forming complexes, where X-ray crystallography or electron microscopy fail.

I will demonstrate the approach on the example of a multi-protein complex responsible for acetylation of histone H3. The complex consists of the fungal histone acetyltransferase Rtt109, the histone chaperones Asf1 and Vps75 and the H3:H4 histone dimer. Rtt109 is required for histone H3 K9, K27 and K56 acetylation in fungi and is thus an attractive drug target in the fight of fungal infections. Rtt109 activity requires two structurally unrelated histone chaperones, Asf1 and Vps75. These proteins activate Rtt109 via different mechanisms, with Rtt109–Asf1 association being necessary for K56 acetylation, and Rtt109–Vps75 association being required for K9 acetylation.

Using our integrative structural biology approach, we explain how Vps75 promotes acetylation of residues in the H3 N-terminal tail: the chaperone engages the disordered H3 tail in fuzzy electrostatic interactions with its own disordered C-terminal domain and thereby confines the H3 tail to a wide cavity faced by the Rtt109 active site. These fuzzy interactions between disordered domains achieve localization of the H3 tail to the catalytic site with minimal loss of entropy, and may represent a universal mechanism for substrate localization in enzymatic reactions involving long, highly-disordered substrates.