

Microsymposium

MS87.O03

Microtubule chemical complexity: mechanism of tubulin modification enzymes

A. Roll-Mecak¹, A. Szyk¹, V. Kormendi¹

¹*Cell Biology and Biophysics Unit, NINDS, National Institutes of Health, Bethesda, USA*

Tubulin is subject to an abundant and diverse set of post-translational modifications that include phosphorylation, acetylation, poly-glutamylolation, poly-glycylation and tyrosination. The highest density and variety of post-translational modifications are found in especially complex microtubule arrays like those of neurons or cilia. Not surprisingly, tubulin modification enzymes have been linked to human diseases including cancers and neurodegenerative disorders. I will present recent data from my lab on the mechanism of action of two tubulin modification enzymes that illustrate two divergent paradigms of tubulin recognition. Tubulin tyrosine ligase (TTL) adds a C-terminal Tyr to the exposed C-terminus of alpha-tubulin as part of a tyrosination/detyrosination cycle present in most eukaryotic cells. We solved the first crystal structure of tubulin tyrosine ligase that revealed how the TTL scaffold supported the expansion of the repertory of tubulin post-translational modification enzymes of the TTL like family that recognize either alpha- or beta-tubulin C-terminal tails. In addition to modifying tubulin, TTL also prevents tubulin from incorporating into microtubules by recognizing a tubulin dimer interface that would otherwise be involved in microtubule lattice interactions. I will also present recent work from my group on the structure and mechanism of action of tubulin acetyltransferase (TAT). TAT acetylates Lys-40 on alpha-tubulin in the microtubule lumen. We solved the 2.7Å structure of TAT bound to its ac-coA substrate as well as the 2.45Å structure of a catalytic inactive TAT mutant that reveals a domain swapped dimer in which the functionally essential N-terminus shows evidence of unprecedented structural plasticity. Implications for catalysis and microtubule stimulation of TAT activity will be discussed.

Keywords: tubulin, post-translational modification, enzyme