Exploring the Crosstalk Between Tubulin Post-Translational Modifications

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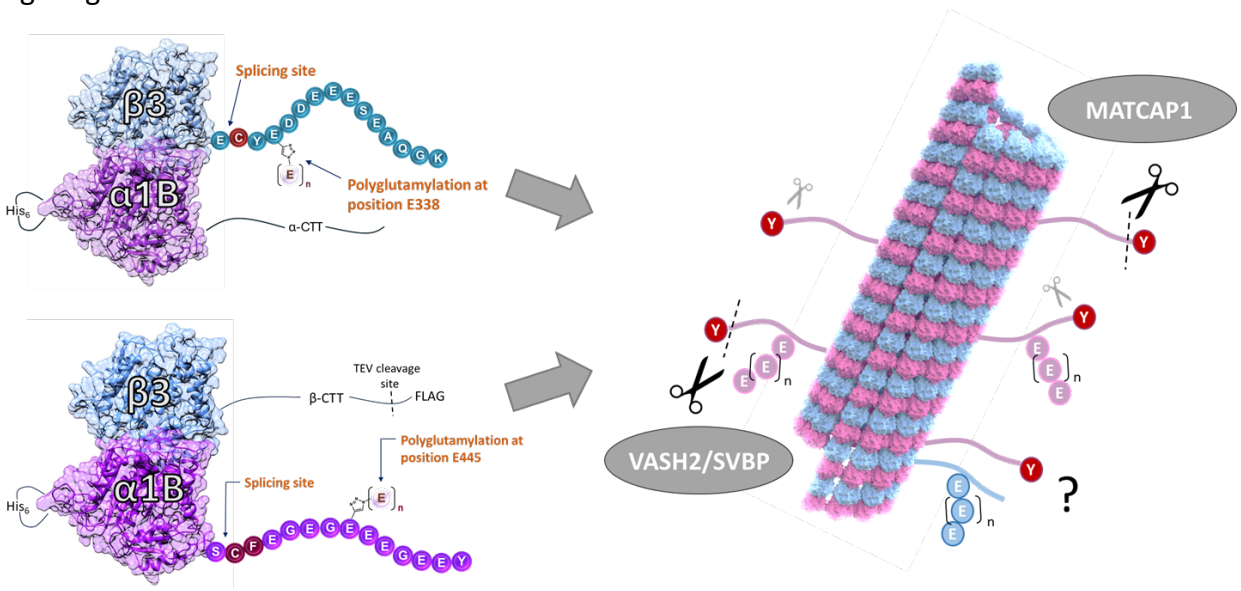
Microtubules are essential protein biopolymers comprised of α- and β-tubulin subunits that constitute the cytoskeleton, centrioles, cilia and other organelles in eukaryotic cells. The biophysical and biochemical properties of microtubules are regulated by a so-called tubulin code: different α/β-tubulin isoforms and various post-translational modifications (PTMs) such as detyrosination/tyrosination, polyglutamylation (polyE) and others. Misregulation of tubulin PTMs is associated with a number of diseases, including neurodevelopmental and respiratory disorders, cardiomyopathies, and cancers.

In our work, we study the role of the tubulin code, in particular the crosstalk between polyE and detyrosination, both critical for cell function and found together on specific microtubules. In earlier work, we developed a method to produce semisynthetic tubulin carrying defined PTMs on α-subunit C-terminal tail (CTT). We showed that polyE upregulates the activity of vasohibins, one of the key enzymes involved in tubulin detyrosination [1].

However, vasohibins are not alone responsible for tubulin detyrosination. Indeed, the recently discovered enzyme, MATCAP1 [2] represents a second carboxypeptidase providing tubulin detyrosination activity. Here, we use semisynthetic microtubule substrates, carrying various degrees of polyE to demonstrate that α-tubulin polyglutamylation downregulates MATCAP1 activity, as opposed to vasohibins.

So far, our semisynthetic approach has been limited to the α-tubulin subunit. Of note, cryoEM structural data [2] indcate that MATCAP might be as well sensitive to PTMs on β-tubulin CTT. To test this hypothesis, I am working on developing novel chemical methods to also introduce PTMs, in particular polyE, into β-tubulin. Moreover, the establishment of these methods would complement the toolkit for investigating the tubulin code in molecular detail.



[1] E. Ebberink, et al. *Nature Chemistry*, **2023**, 15.8, 1179–1187.
[2] Landskron, Lisa, et al. *Science*, **2022**, 376.6595, eabn6020.