LABORATORY OF

BIOLOGY OF CYTOSKELETON

Microtubules, γ-tubulin complexes, signal transduction

Pavel Dráber

more information

e-mail

The long-term research programme of the laboratory has been focused on studying the structure-function relationships of microtubule (MT) proteins in cells under normal and pathological conditions. The organization of dynamic MT networks is controlled by MT organizing centres (MTOCs). One of the key components of MTOCs is γ-tubulin, which is necessary for nucleation of MTs. Our current work focuses on understanding the modulation of MT organization by signal transduction molecules. Our results demonstrate that activation of bone marrow-derived mast cells (BMMCs) induces rapid and transient MT reorganization that is dependent both on protein tyrosine kinases and $Ca^{2+}$and diacylglycerol-regulated protein kinase C (cPKC). Suppression of MT formation in later stages of BMMC activation is regulated by protein tyrosine phosphatase 1 (SHP-1), which forms complexes with γ-tubulin ring complex proteins. MT regrowth and phenotypic rescue experiments showed that SHP-1 represents a negative regulator of MT nucleation. The modulation is due to the changes in γ-tubulin accumulation on the centrosomes. We have shown that two human γ-tubulins (genes *TUBG1, TUBG2*) differ in their properties, but both associate with mitochondrial membranes. Although γ-tubulin 2 accumulates in the adult brain, γ-tubulin 1 remains the major isotype in various brain regions. Differentiation of SH-SY5Y human neuroblastoma cells or oxidative stress induced by mitochondrial inhibitors resulted in upregulation of γ-tubulin 2, while the expression of γ-tubulin 1 was unchanged. These data indicate that in the face of predominant γ-tubulin 1 expression, the accumulation of γ-tubulin 2 in mature neurons and neuroblastoma cells during oxidative stress may denote a prosurvival role of γ-tubulin 2 in the neurons. We have also shown that *TUBG1* missense variants linked with malformations of cortical development disrupt microtubule dynamics but not neurogenesis. Finally, we were the first to report that the self-assembly of tubulin can be controlled by intense nanosecond pulsed electric fields, which modulate tubulin conformations.

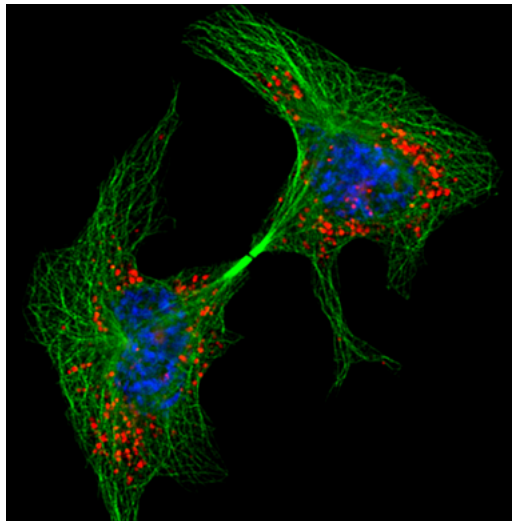

Figure 1. Rat basophilic RBL-2H3 cells stained for microtubules (green), serotonin granules (red) and nuclei (blue).

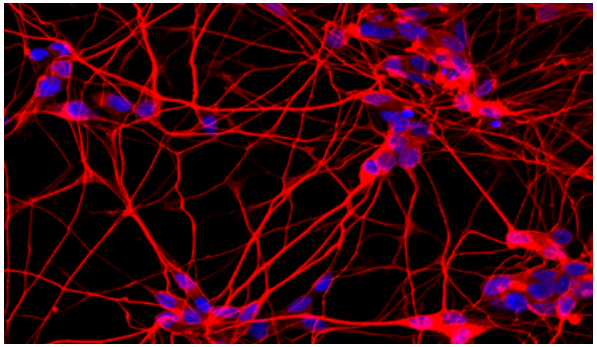

Figure 2. Human neuroblastoma SH-SY5Y cells differentiated by all-trans retinoic acid. Staining for βIII-tubulin (red) and nuclei (blue).

Selected publications:

1. Klebanovych A, Sládková V, Sulimenko T, Vosecká V, Rubíková Z, Čapek M, Dráberová E, Dráber P*, Sulimenko V* (2019) Regulation of microtubule nucleation in mouse bone marrow-derived mast cells by protein tyrosine phosphatase SHP-1. ***Cells*, 8**:e345.
2. Chafai DE*, Sulimenko V, Havelka D, Kubínová L, Dráber P, Cifra M* (2019) Reversible and irreversible modulation of tubulin self-assembly by intense nanosecond pulsed electric fields. ***Adv Mater*, 31**:e1903636.
3. Ivanova E, Gilet JG, Sulimenko V, Duchon A, Rudolf G, Runge K, Collins SC, Asselin L, Broix L, Drout N, Tilly, P, Nusbaum P, Vincent A, Magnant W, Skory V, Birling MC, Pavlovic G, Godin JD, Yalcin B, Herault Y, Dráber P, Chelly J, Hinckelmann MV* (2019) *TUBG1* missense variants underlying cortical malformations disrupt neuronal locomotion and microtubule dynamics but not neurogenesis. ***Nat Commun*, 10**:e2129.
4. Rubíková Z, Sulimenko V, Paulenda T, Dráber P* (2018) Mast cell activation and microtubule organization is modulated by miltefosine through protein kinase C inhibition**.** ***Front Immunol*, 9**:e1563.
5. Dráberová E, Sulimenko V, Vinopal S, Sulimenko T, Sládková V, D'Agostino L, Sobol M, Hozák P, Křen L, Katsetos CD, Dráber P*(2017) Differential expression of human γ-tubulin isotypes during neuronal development and oxidative stress points to γ-tubulin 2 prosurvival function. ***FASEB J*, 31**:1828-1848.

In the picture: 1. Sulimenko Vadym | 2. Rubíková Zuzana | 3. Vosecká Věra | 4. Sládková Vladimíra | 5. Sulimenko Tetyana | 6. MIchová Irena | 7. Klebanovych Anastasiya | 8. Dráberová Eduarda | 9. Dráber Pavel