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Ecole Polytechnique
Amphithéâtre Becquerel

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Regulation of microtubule dynamics and functions group
Institut Curie, Bat 110, 91405 Orsay cedex
https://science.institut-curie.org/research/biology-chemistry-of-radiations-cell-signaling-and-cancer-axis/umr3348-genotoxic-stress-and-cancer/team-janke/

Role of tubulin polyglutamylation in neuronal homeostasis

Microtubules are key components of the neuronal cytoskeleton and play pivotal roles in all aspects of neuronal physiology: neuronal development, migration and connectivity, and axonal transport. It is thus not surprising that microtubule dysfunctions are associated with neurodevelopmental and neurodegenerative disorders. Yet, little is known about the control of microtubule functions within a single neuron. An emerging molecular mechanism that could control microtubule those functions are tubulin posttranslational modifications, and particularly polyglutamylation, which decorates neuronal microtubules.

To understand the role of this modification in neurons, I have generated knockout mice with either reduced or excessive polyglutamylation. In these mice, deregulation of polyglutamylation invariably leads to neurodegeneration. Together with a PhD student we have shown that polyglutamylation controls axonal transport, a microtubule-based process essential for neuronal survival. Finally, we discovered that excessive polyglutamylation is responsible for infantile-onset neurodegeneration, demonstrating its importance for human health.

By combining different approaches, such as in-vitro reconstitutions of microtubule assemblies, primary neuronal cell culture and mouse models, I now aim at determining the mechanisms by which polyglutamylation controls microtubule architecture and functions in neurons, and how this affects neuronal homeostasis, neuronal activity and connectivity, overall brain architecture as well as mouse behaviour.