Abstract

Intracellular transport of mitochondria and other cell components along microtubules is fundamental in all cells, especially in neurons. The anterograde mitochondrial transport is driven by molecular motor kinesin-1 (KIF5), which is connected to mitochondria through the adaptor protein TRAK1. Recently, a less explored protein, optineurin (OPTN), has emerged as a novel regulator of this transport. Together with our collaborators, we show in our recent study that anterograde mitochondrial transport in mice is regulated by OPTN. Additionally, we show that OPTN is a microtubule-associated protein (MAP) that can interact with the KIF5B-TRAK1 complex, enhancing its run length, run time, and landing rate on microtubules. Since OPTN was just discovered as a new MAP, little is known about its interaction with microtubules. In this work, we show how OPTN interacts with differently post-translationally modified microtubules and different microtubule isoforms. Using an in vitro reconstitution assay, we show that OPTN prefers unmodified over highly post-translationally modified microtubules and forms regions of high affinity (patches) on them. Furthermore, OPTN shows isoform specific binding with significantly higher affinity to the α1β4 isoform compared to the α1β3 isoform. Unlike its interaction with unmodified microtubules, OPTN does not form patches on the α1β4 and α1β3 isoforms, instead, it covers the microtubules homogenously. Together, our results suggest that distinct tubulin isoforms could have increased affinity to themselves, and during microtubule assembly, they could preferentially interact with themselves, which would result in a formation of distinct regions on microtubules. These distinct regions could then influence the binding of MAPs, like OPTN, and molecular motors, and by that also regulate intracellular transport.

Key words: Optineurin, OPTN, OPTN patch, microtubules, isoforms, α1β4, α1β3, post-translational modifications, PTMs, microtubule-associated proteins, MAPs, molecular motors, kinesin-1, TRAK1, intracellular transport