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Tropomyosins in the healthy and diseased nervous system

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ABSTRACT

Regulation of the actin cytoskeleton is dependent on a plethora of actin-associated proteins in all eukaryotic cells. The family of tropomyosins plays a key role in controlling the function of several of these actin-associated proteins and their access to actin filaments. In order to understand the regulation of the actin cytoskeleton in highly dynamic subcellular compartments of neurons such as growth cones of developing neurons and the synaptic compartment of mature neurons, it is pivotal to decipher the functional role of tropomyosins in the nervous system. In this review, we will discuss the current understanding and recent findings on the regulation of the actin cytoskeleton by tropomyosins and potential implication that this has for the dysregulation of the actin cytoskeleton in neurological diseases.

Contents

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1. Introduction

Tropomyosins (Tpm) are a family of actin-associated proteins that play a major role in the regulation of the actin cytoskeleton. Tpm have a coiled-coil structure and form head-to-tail polymers along the main groove of the actin filament. There are four mammalian *Tpm* genes; *TPM1*, *TPM2*, *TPM3* and *TPM4,* which can give rise to over 40 different Tpm isoforms by alternative exon splicing [see (Gunning et al., 2008) for review]. Tpm was first identified in striated muscle (Bailey, 1946) and its role in muscle contraction has been well characterised. However, the role of different Tpm isoforms in regulating the actin cytoskeleton of non-muscle cells is still not entirely clear.

In neurons, the actin cytoskeleton has been implicated in almost every crucial cellular process, including neurite outgrowth, branching and synapse formation. The interaction with a large number of actin-associated proteins diversifies the physical and dynamic properties of actin filaments, giving it versatility in the regulation of cellular structure and function. Different Tpm isoforms interact uniquely with the cytoskeleton, allowing for spatially and temporally controlled regulation of actin filament dynamics. Tpms also interact with many different actin-binding proteins (ABPs), creating a complex Tpm-actin-ABP system which works to maintain normal cell function. Such an intricate system provides the cell with many benefits. However, when a single component becomes dysregulated, it can create a cascade of reactions that ultimately result in disease.

Tpms can regulate the interaction of other actin binding proteins (ABPs) and actin filaments by recruiting ABPs in an isoform specific manner. In neuronal cells, isoforms from three *Tpm* genes are found (*TPM1*, *TPM3* and *TPM4*, Fig. 1). Five isoforms from the *TPM1* gene are expressed in the brain: Tpm1.8, 1.9, 1.10, 1.11 and 1.12 (Dufour et al., 1998; Geeves et al., 2015). Alternate splicing of the *TPM3* gene generates the most diverse array of Tpm isoforms within the brain, leading to expression of Tpm3.1, 3.2, 3.3, 3.4, 3.5, 3.7, 3.8 and 3.9 (Dufour et al., 1998; Vrhovski et al., 2003). The *TPM4* gene product Tpm4.2 is found in the brain (Had et al., 1994). The isoform-specific effects of Tpm can be manipulated to impact cellular function and potentially overcome structural and functional changes in diseased or damaged cells. The isoform specific structures of Tpm are already being utilised in other fields, with the Tpm3.1 isoform being targeted as a chemotherapeutic target (Stehn et al., 2013).

In this review, we will discuss the developmental and spatial regulation of Tpm expression in the central nervous system (CNS), with a focus on the role of Tpm in neurite outgrowth, and its localisation and function at the synaptic connections. We will finish by outlining the possible mechanisms by which Tpm could be involved in injury and neurological disease, postulating how these could be manipulated to promote CNS repair.

2. Tropomyosins – key regulators that define the physical and dynamic properties of actin filaments

The actin cytoskeleton is regulated by a wide variety of actin binding proteins (ABPs) which provide it with structural and functional diversity. These ABPs can be regulated and recruited by Tpm in an isoform specific manner. Actin related protein 2/3 (Arp2/3) is a protein complex which nucleates existing actin filaments to form new branches. Advancement of the leading edge at the lamellipodium is largely driven by Arp2/3 activity which generates dense, branched F-actin networks. It has been shown that Tpm1.6, Tpm1.8, Tpm1.9 and Tpm3.1 can inhibit this Arp2/3 mediated actin filament branching (Blanchoin et al., 2001; Brayford et al., 2016; Kis-Bicskei et al., 2013) (Fig. 2A). It is hypothesised that Tpm inhibits the ability of actin filaments to act as secondary activators for Arp2/3 and potentially competes with Arp2/3 for actin binding sites (Blanchoin et al., 2001). Silencing of Tpm1.8 and Tpm1.9 results in increased levels of Arp2/3 at the cell periphery, and inhibition of Arp2/3 leads to increased Tpm1.8 and 1.9 expression. This finding suggests that Tpm1.8 and Tpm1.9 are recruited to the leading edge to serve as antagonists for Arp2/3 activity, promoting stabilisation of the F-actin network (Brayford et al., 2016). In contrast, Tpm1.12 supports Arp2/3 mediated actin branching (Kis-Bicskei et al., 2013).

Members of the actin filament severing protein family ADF/cofilin compete with Tpms for actin binding in a Tpm isoform dependent manner (Bernstein and Bamburg, 1982; Bryce et al., 2003; Curthoys et al., 2014; Ono and Ono, 2002) (Fig. 2B). Whereas Tpm1.12 overexpression allows binding of ADF/cofilin to actin filaments, overexpression of Tpm3.1 and Tpm4.2 cause an increase in phosphorylated, inactive ADF/cofilin and therefore leading to a reduction in ADF/cofilin-actin binding (Bryce et al., 2003; Curthoys et al., 2014). Similar to Tpm1.8 and Tpm1.9, Tpm3.1 also inhibits Arp2/3 (Kis-Bicskei et al., 2013) activity which suggests that it might be competing with both Arp2/3 and ADF/cofilin to maintain stable actin filaments.

Tropomodulins (Tmods) are a family of actin-associated proteins that stabilise actin filaments by capping them from the pointed-end, preventing both elongation and depolymerisation from that end [the family of tropomodulins has been extensively reviewed recently, see (Fath, 2013; Yamashiro et al., 2012)]. *In vitro*, Tmod capping has been shown to prevent ADF/cofilin mediated actin depolymerisation (Yamashiro et al., 2008). Tmod1 has high affinity for Tpm1.8 and Tpm3.1 (Yamashiro et al., 2014) (Fig. 2C) and associates with actin filaments in lamellipodia and growth cones (Fath et al., 2011; Moroz et al., 2013). Tpm1.12 and Tpm3.1, along with Tpm1.8, have high affinity for Tmod2 (Fig. 2C), which displays predominantly cytoplasmic localisation (Fath et al., 2011; Moroz et al., 2013; Watakabe et al., 1996). Both of these Tmod isoforms have been implicated as regulators of neurite outgrowth (Fath et al., 2011; Moroz et al., 2013). Tmod2 inhibits neurite extension, while Tmod1 only inhibits the formation of new neurites without affecting existing ones (Fath et al., 2011). In differentiating PC12 cells, expression of Tmod2 led to a significant reduction in neurite outgrowth (Moroz et al., 2013). Furthermore, Tmod2 knockout mice display learning and memory deficits along with increased long-term potentiation (LTP). These results indicate that Tpm isoforms and Tmod2 may indirectly regulate the F-actin dynamics which underlie synaptic plasticity (Cox et al., 2003).

While it is clear that Tpm interacts with many different ABPs, the mechanism by which Tpm isoforms are recruited to different actin filaments is not fully understood. A recently proposed model, based on studies in yeast, suggests that Tpm sorting is regulated by formins (Johnson et al., 2014). Formins are a class of potent actin filament nucleators, similar to Arp2/3. While Arp2/3 generates branched actin networks, formins promote the formation and elongation of straight actin filaments. Formins bind to the barbed end of actin filaments to initiate or elongate the filament (Li and Higgs, 2003; Wasserman, 1998). It has been postulated that formin can nucleate actin filaments and then determine which Tpm isoform(s) will be recruited to that filament (Gunning et al., 2015; Johnson et al., 2014). Formins can also associate laterally with actin filaments, possibly modulating their affinity for various Tpm isoforms (Bugyi et al., 2006; Martin and Chang, 2006). Tpm itself can regulate the interaction between formin and actin filaments, indicating that the Tpm-formin-actin association is synergistic and highly dynamic (Ujfalusi et al., 2012; Wawro et al., 2007).

Fascin is an actin bundling protein that localises to filopodia and is involved in growth cone morphogenesis (Cohan et al., 2001; Ishikawa et al., 2003). Actin filament populations bundled by fascin are more resistant to inhibitory treatments, using the repulsive