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MYO18A: An unusual myosin

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ABSTRACT

MYO18A is a divergent member of the myosin family characterized by the presence of an amino-terminal PDZ domain. MYO18A has been found in a few different complexes involved in intracellular transport processes. MYO18A is found in a complex with LURAP1 and MRCK that functions in retrograde treadmilling of actin. It also has been found in a complex with PAK2, βPIX, and GIT1, functioning to transport that protein complex from focal adhesions to the leading edge. Finally, a high proportion of MYO18A is found in complex with GOLPH3 at the *trans* Golgi, where it functions to promote vesicle budding for Golgi-to-plasma membrane trafficking. Interestingly, MYO18A has been implicated as a cancer driver, as have other components of the GOLPH3 pathway. It remains uncertain as to whether or not MYO18A has intrinsic motor activity. While many questions remain, MYO18A is a fascinatingly unique myosin that is essential in higher organisms.

Contents

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1. Introduction

MYO18A is an unconventional myosin that has been implicated in multiple cellular processes. It has roles in retrograde treadmilling of actin and in the function of focal adhesions. It also plays an important role at the Golgi as part of the machinery for vesicle exit for Golgi-to-plasma membrane trafficking. There remain many questions about its function and controversies in the literature that have yet to be resolved. Nevertheless, it is clear that MYO18A is an interesting protein whose study promises to provide insight into a range of biology.

2. Discovery of MYO18A as a novel PDZ-containing myosin

MYO18A was first identified in 2000 by Obinata and colleagues in a screen for genes that are up-regulated in stromal cell lines with increased capacity to support hematopoietic stem cells (presumably via secretion of paracrine growth factors) (Furusawa et al., 2000). Their further characterization of MYO18A (referred to as MysPDZ) reported ubiquitous expression in all tissues, detection of multiple splice forms, and subcellular localization of both the endogenous protein and exogenously expressed, tagged protein at the ER and Golgi (Furusawa et al., 2000; Mori et al., 2003, 2005). Analysis of MYO18A domain structure revealed a core myosin-homology region, closest in homology to myosin II but fairly divergent, an extended coiled-coil region at the C-terminus, and an extended N-terminus (Fig. 1). The N-terminal portion of the protein was recognized to contain a Lys-Glu (KE) repeat region. In addition, unique among myosins, the MYO18A N-terminal portion includes a PDZ domain, which is a critical defining feature of MYO18A across species. PDZ domains typically enable protein-protein interactions often by binding to a PDZ motif found at the C-terminus of some proteins. However, there also are examples of PDZ domain interactions with internal protein sequences (Harris and Lim, 2001) and with lipids (Zimmermann, 2006). PDZ domains are frequently observed in proteins involved in intracellular signal transduction pathways. Thus, even early on it seemed that MYO18A may be involved in signaling. Bolstering this idea, unbiased analysis of protein phosphorylation in myeloblastic cells in response to macrophage colony stimulating factor (CSF-1) identified prominent tyrosine phosphorylation of MYO18A (Cross et al., 2004). Indeed, subsequent unbiased proteomic analyses have identified abundant phosphorylation of MYO18A on Ser, Thr, and Tyr, in addition to other post-translational modifications such as lysine ubiquitination, acetylation, and methylation (Hornbeck et al., 2015). The function, if any, of these modifications remains largely unknown.

3. A role for MYO18A in retrograde actin treadmilling

Tan et al. identified MYO18A in a complex with Myotonic dystrophy kinase-related CDC42-binding kinase (MRCK) and Leucine-rich adaptor protein 1 (LURAP1, also known as LRAP35a) (Tan et al., 2008). Unbiased experiments to identify proteins

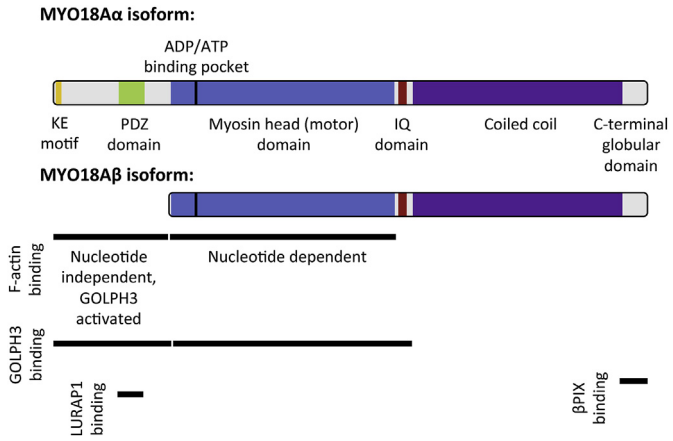

Fig. 1. Protein domain structure and protein interaction sites of MYO18A. See text for details and references.

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