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Review

A formin-g role during development and disease

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ABSTRACT

Several different protein families were shown to be involved in the regulation of actin filament formation and have been studied extensively in processes such as cell migration. Among them are members of the formin family, which tend to promote the formation of linear actin filaments. Studies in recent years, often using loss of function animal models, have indicated that formin family members play roles beyond cell motility in vitro and are involved in processes ranging from tissue morphogenesis and cell differentiation to diseases such as cancer and cardiomyopathy. Therefore the aim of this review is to discuss these findings and to start putting them into a subcellular context.

Introduction

The actin cytoskeleton is important for scaffolding as well as for movement in all eukaryotic cells. Globular actin monomers are polymerised to form long filaments, a process that is regulated by a wide range of actin associated proteins (Pollard and Cooper, 2009). It is through the dynamic control of actin filaments that cell shape, cell migration and cell contraction are determined. Since the nucleation of actin filaments is an energetically unfavourable process, three main families of actin nucleation factors have been defined: (1) the Arp2/3 complex, which operates together with downstream nucleation-promoting factors such as N-WASP, (2) WH2-domain containing proteins such as Spire and leimodin and (3) the formin family (Campellone and Welch, 2010). The Arp2/3 complex is responsible for the formation of branched actin filaments at the leading edge of motile cells (reviewed in Pollard, 2007). Leiomodin is known to be responsible for the maintenance of sarcomeres in muscle as well as its actin nucleation properties (Chereau et al., 2008). Both types of actin filament promoting factors act at the pointed end, which is the slower growing end.

Members of the formin family are unique in that they tend to promote actin assembly at the fast growing barbed end. They are thought to operate in a processive way, moving along as the actin filament grows (Goode and Eck, 2007). In addition to facilitating the addition of actin monomers, it is also the ability of formins to prevent the association of actin capping proteins that is thought to be responsible for the promotion of actin filament formation (Paul and Pollard, 2009).

Formins: molecular characteristics

Formin family proteins are defined by the presence of the formin-homology domains 1 and 2 (FH1 and FH2) in the C-terminal half of the molecule (Faix and Grosse, 2006; for a schematic representation of the domain layout of a typical formin molecule see Fig. 1) and have been grouped into eight different subfamilies (Campellone and Welch, 2010; Schönichen and Geyer, 2010). These can be broadly divided into two main categories, diaphanous related formins (DRFs) and non-DRFs. DRFs, so called because of the initial discovery of FH domains in the diaphanous gene of *Drosophila*, are characterised by the possession of an N-terminal GTPase binding domain (GBD). These include mouse diaphanous-related formin mDia1-3, formin like proteins FRL 1-3, formin homology 2 domain containing FHOD1 and FHOD3 and dishevelled-associated activator of morphogenesis DAAM1 and DAAM2. Non-DRFs such as Formin-1 and Formin-2 (FMN1 and FMN2) lack obvious GBDs, but can possess additional functional domains such as a PDZ domain in the case of Delphilin. Inverted formins INF1 and INF2 (also called WH2-domain containing formin) have their FH1 and FH2 domains shifted more towards the N-terminus of the molecule (Campellone and Welch, 2010; Schönichen and Geyer, 2010).

So far most of our knowledge on the function and activation of formins has been gained by studying the different members of the DRF family, in particular mDia1 (for recent reviews on formins see Goode and Eck, 2007; Chesarone et al., 2010; Schönichen and Geyer, 2010). A sequence of reasonably conserved domains along a DRF

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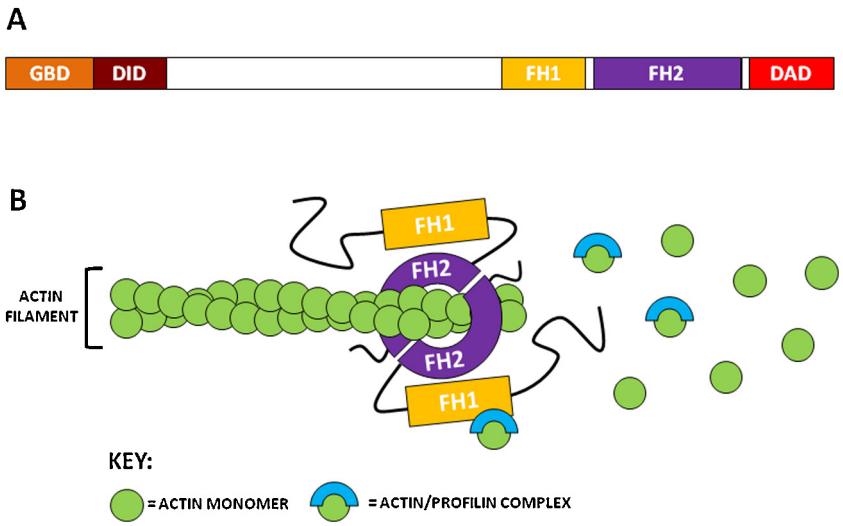

Fig. 1. Schematic representation of a formin molecule and its mediation of actin filament assembly. (A) The domain arrangement that characterises DRF family monomers. GBD, GTPase binding domain; DID, diaphanous inhibitory domain; FH1, formin homology domain 1; FH2, formin homology domain 2; DAD, diaphanous autoregulatory domain. (B) The FH1 domains are thought to reel in actin via their interaction with profilin, while the FH2 domains are responsible for creating doughnut shaped homodimers in which actin nucleation can occur. Actin monomers are shown in green, profilin in blue, the FH1 domain in yellow and the FH2 domain in purple.

molecule defines its function. The N-terminal GBD is often responsible for correct subcellular localisation within the cell, although in the case of a striated muscle specific splice variant of FHOD3 the phosphorylation of amino acids in the FH2 domain has been shown to be crucial for myofibrillar targeting in neonatal rat cardiomyocytes (Iskratsch et al., 2010). In addition, binding of a small GTPase to the GBD domain is required for the activation of most DRF family members, since it relieves the intramolecular interaction of the diaphanous inhibitory domain (DID) and the diaphanous autoregulatory domain (DAD), which otherwise obscure access to the actin polymerisation site (Nezami et al., 2010; Otomo et al., 2010). However, the lack of an obvious GBD, as described for FMN1 and FMN2, does not exclude interaction and activation by a small GTPase, since the *Drosophila* formin Cappuccino (Capu) is activated by Rho1 binding, too (Rosales-Nieves et al., 2006). The FH1 domain is responsible for binding to profilin, the protein responsible for recruiting the actin to be polymerised (Paul and Pollard, 2009). Two FH2 domains form a doughnut shaped homodimer which is essential for the actin nucleation process (Xu et al., 2004). Recent structural studies showed that full length mDia1 exists as a dimer already in its inactive form and that this dimerisation is not only mediated by the FH2 domain but also by a second dimerisation domain downstream of the DID domain (Maiti et al., 2012). Autoinhibition is due to the steric obstruction of actin binding to the FH2 dimer, in addition the binding of RhoA to the GBD only leads to a partial activation of mDia1 (Maiti et al., 2012). For some members of the DRF family such as FHOD1 and FHOD3 no interaction with a small GTPase seems to be required for activation and it is sufficient if three amino acids in the DAD domain are phosphorylated by ROCK to get a functional response (Iskratsch et al., 2013a; Takeya et al., 2008).

Different subcellular tasks of formins

Most cells co-express several formins, which show distinct subcellular targeting and activity (see Fig. 2, which collates available data for endogenous as well as for overexpressed epitope/GFP-tagged formins and also Table 1 for tissue-specific expression). It is known that DRFs are essential for the formation of filopodia in order to aid cell migration (for reviews see Pollard et al., 2000; Gardel et al., 2010; Le Clainche and Carlier, 2008). DRFs were also shown

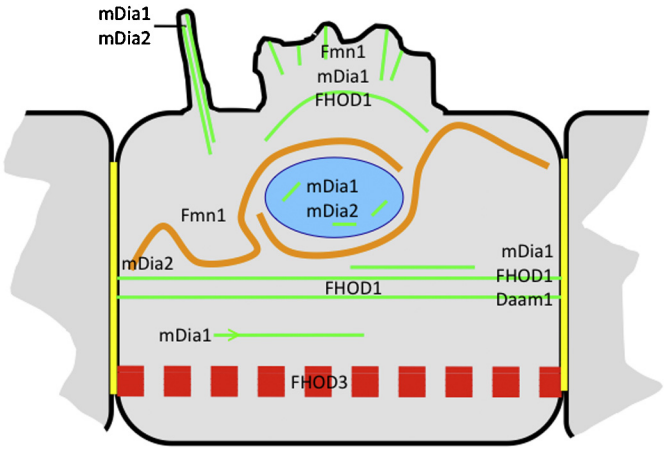

Fig. 2. Different DRF formins target to distinct subcellular regions. Schematic representation of a cell, showing the subcellular localisation of a subset of formins from the DRF family. Both endogenous formin localisation data as well as data from epitope/GFP-tagged formins are included in this representation. F-actin is depicted in green, microtubules in orange, the nucleus is blue, cell–cell contacts are yellow and myofibrils are shown in red.

to be required during cell division to help mediate the assembly of the contractile ring for cytokinesis (Faix and Grosse, 2006). In addition, formins are known to be involved in the formation of adherens junctions, an actin-anchoring type of cell–cell contact (Kobielak et al., 2004; Sahai and Marshall, 2002). In many cases formin activity is thought to be triggered in close proximity to the plasma membrane, partially due to the interaction with a membrane-associated small GTPase and subsequent release from the autoinhibitory state. Different formins have evolved distinct structural domains, which probably define their interaction with a particular small GTPase and contribute to their biological function. For example while mDia1 shows a classical Rho binding motif and is activated by Rho (Lammers et al., 2008), FHOD1 displays an ubiquitin-like superfold, which probably explains why it preferentially interacts with Rac (Schulte et al., 2008). The subcellular compartment at the membrane may also function as a safeguard, since the interaction of mDia with phospholipids renders the molecule inactive for actin filament assembly (Ramalingam et al., 2010). So far most of the

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