Biochimica et Biophysica Acta 1803 (2010) 226–233

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

The role of formins in human disease

Aaron D. DeWard [a,1], Kathryn M. Eisenmann [b,1], Stephen F. Matheson [a,c], Arthur S. Alberts [a,*]

[a] Laboratory of Cell Structure and Signal Integration, Van Andel Research Institute, Grand Rapids, MI 49503, USA
[b] Department of Biochemistry and Cancer Biology, The University of Toledo, 3000 Arlington Avenue, Toledo, OH 43614-2598, USA
[c] Calvin College, Grand Rapids MI 49503, USA

ARTICLE INFO

Article history:
Received 21 October 2009
Received in revised form 6 November 2009
Accepted 10 November 2009
Available online 24 November 2009

Keywords:
Formin
Actin
Microtubule
Rho GTPase
Non-syndromic deafness
Cancer
Myelodysplasia
Tumor suppression
Premature ovarian failure
Limb deformity
Metastasis
Immune response
Oncosome
Microvesicle

ABSTRACT

Formins are a conserved family of proteins that play key roles in cytoskeletal remodeling. They nucleate and processively elongate non-branched actin filaments and also modulate microtubule dynamics. Despite their significant contributions to cell biology and development, few studies have directly implicated formins in disease pathogenesis. This review highlights the roles of formins in cell division, migration, immunity, and microvesicle formation in the context of human disease. In addition, we discuss the importance of controlling formin activity and protein expression to maintain cell homeostasis.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Formin family proteins—so-called because of conserved formin-homology-1 and -2 (FH1 and FH2) domains—have emerged as key regulators of actin and microtubule cytoskeletal dynamics during cell division and migration. The FH1 and FH2 domains were identified by Castrillon and Wasserman in the initial characterization of the *Diaphanous* gene in *Drosophila* [1], and both domains participate in the control of cytoskeletal remodeling. The proline-rich FH1 domains have been shown to bind to numerous WW- and SH3-domain containing proteins in addition to profilin-actin, which contributes to the ability of formins to produce non-branched actin filaments. FH2 domains dimerize, then nucleate and processively elongate linear actin filaments by associating with their growing barbed (+) ends. These FH2 dimers create an environment that favors actin monomer addition to generate actin filaments.

While formins are important for actin remodeling events, formins can also modulate microtubule dynamics [2] in at least two different ways. Diaphanous-related formins (DRFs), the family of formins most closely related to the canonical formin Diaphanous, bind directly to microtubules to promote their stabilization [3]. In addition, mammalian DRF (mDia) proteins have been shown to associate with microtubule-end binding proteins EB1 and APC [4]. APC is the product of the adenomatous polyposis coli (*APC*) familial colon cancer tumor suppressor gene, and its role in disease progression may be mediated in part by mDia family proteins. Emerging evidence suggests that the formin mDia1 possesses tumor suppressor activity [5], again pointing to a role for formins in cancer formation.

Defects in cytoskeletal remodeling proteins have previously been implicated in malignancy [6] and the aforementioned association between mDia proteins and tumor suppression may point to specific roles for formins in cancer and other diseases. However, despite the significant roles formins play in cell biology and development [7], there have been relatively few studies that directly link formins with disease pathogenesis. This review highlights the existing body of

* Corresponding author. Laboratory of Cell Structure & Signal Integration, Van Andel Research Institute, 333 Bostwick Ave., N.E. Grand Rapids, MI 49503, USA.
E-mail address: Art.Alberts@vai.org (A.S. Alberts).
[1] Equal contributors.

0167-4889/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2009.11.006

knowledge that suggests defects in formin gene and gene product function contributes to disease.

2. Cytoskeletal remodeling and the cell cycle

Inappropriate cell cycle regulation and cell division are often responsible for the cellular changes that lead to human disease. Changes in cell morphology, chromosome segregation, and vesicular trafficking are all fundamental events that occur during cell division. Each of these events are governed by cytoskeletal remodeling, and it is not surprising then that formins are centrally involved in many aspects of cell division. In fact, one of the best-characterized roles for formins is a necessary function during cytokinesis [1,8,9].

Cytokinesis occurs in the last stage of cell division to physically separate the mother cell into two daughter cells. This process requires the formation of an actin-rich contractile ring that constricts to induce plasma membrane invagination. Completion of cytokinesis is marked by abscission of the daughter cells. Importantly, disruption of formin function by mutation or genetic deletion often results in cytokinesis failure (Fig. 1). This initial discovery was made in *Drosophila* after loss of the *Dia* allele led to aneuploidy in germ cells [1]. Subsequent work in other species has shown that numerous formins play a critical role in cytokinesis [7].

Failure to divide the daughter cells after karyokinesis results in a tetraploid cell. Surviving tetraploid cells are prone to genomic instability, widely thought to contribute to cancer initiation and progression [10]. Therefore, inappropriate control of formin function or expression in humans may be a critical event in cancer development. However, there is no evidence that directly links cytokinesis failure with cancer as a consequence of defective formin function, despite the conserved role for formins in cytokinesis.

As mentioned previously, formins can also modulate microtubule dynamics. How formins stabilize microtubules is reviewed in detail by Bartolini and Gundersen [2]. In the context of cell division, microtubule stabilization is required to facilitate chromosome segregation and midbody formation [11]. mDia1 has been shown to localize to spindle microtubules in dividing HeLa cells [12]. However, the contribution of mDia function toward spindle assembly and dynamics remains unclear. mDia1 and mDia2 have also been shown to decorate the midbodies of dividing cells [13]. The midbody, a dense region of stable microtubules at the site of abscission, helps coordinate vesicle trafficking to promote the membrane remodeling required for cell separation. It is likely that formin-mediated microtubule stabilization contributes to the trafficking events during cell division, especially considering that formins control vesicle trafficking in other cellular contexts as well [14–16].

In summary, formin activity is critical for proper cell division and thus for the maintenance of genomic integrity during cell division. Future studies are likely to link formins with cancer initiation or other diseases directly, given the fundamental role of formins during cytokinesis.

3. Formins in cancer cell migration and invasion

Mammalian cells display remarkable capacities for migration, invasion, and morphological plasticity, and these attributes make possible numerous biological processes of central interest in the understanding of development, homeostasis and disease. Cells of the immune system, in particular, are capable of precisely targeted homing and invasion of tissues; cells in metastatic cancer are similarly capable of migration and invasion. These processes are known to depend on dynamic modulation of the cytoskeleton. A thorough understanding of these processes is essential for progress in diagnosis

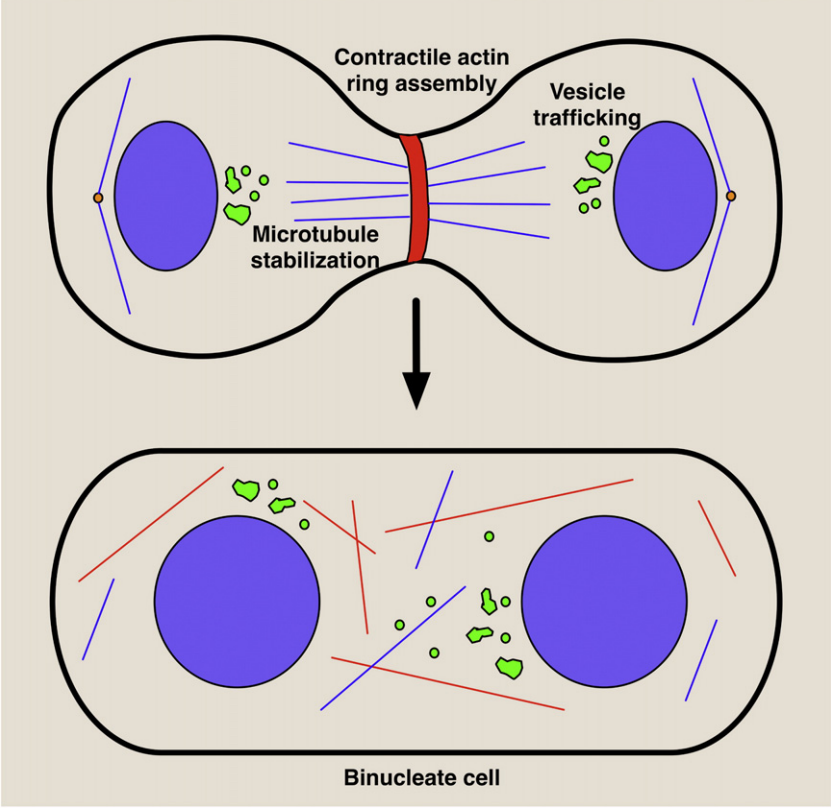

Fig. 1. Formins in cytokinesis. Formins are required for cytokinesis through the assembly of the contractile actin ring. The ability of formins to stabilize microtubules and control vesicle trafficking may also be a required formin function during cytokinesis. Loss of formin activity or deregulation of formin activity has been shown to interfere with cytokinesis and lead to binucleate cells, which can result in chromosome instability.

Download English Version:

https://daneshyari.com/en/article/1951043

Download Persian Version:

https://daneshyari.com/article/1951043

Daneshyari.com