Available online at www.sciencedirect.com
ScienceDirect
Biochimica et Biophysica Acta 1773 (2007) 642–652
Biochimica et Biophysica Acta BBA
www.elsevier.com/locate/bbamcr

Review

Regulation of the actin cytoskeleton in cancer cell migration and invasion

Hideki Yamaguchi [a,*], John Condeelis [a,b,*]

[a] Department of Anatomy and Structural Biology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA
[b] Analytical Imaging Facility, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA

Received 1 February 2006; received in revised form 21 June 2006; accepted 12 July 2006
Available online 14 July 2006

Abstract

Malignant cancer cells utilize their intrinsic migratory ability to invade adjacent tissues and the vasculature, and ultimately to metastasize. Cell migration is the sum of multi-step processes initiated by the formation of membrane protrusions in response to migratory and chemotactic stimuli. The driving force for membrane protrusion is localized polymerization of submembrane actin filaments. Recently, several studies revealed that molecules that link migratory signals to the actin cytoskeleton are upregulated in invasive and metastatic cancer cells. In this review, we summarize recent progress on molecular mechanisms of formation of invasive protrusions used by tumor cells, such as lamellipodia and invadopodia, with regard to the functions of key regulatory proteins of the actin cytoskeleton; WASP family proteins, Arp2/3 complex, LIM-kinase, cofilin, and cortactin.

Keywords: Cell motility; Lamellipodia; Invadopodia; WASP family; Cofilin; Cortactin

1. Introduction

Cell migration is required for many biological processes, such as embryonic morphogenesis, immune surveillance, and tissue repair and regeneration. Aberrant regulation of cell migration drives progression of many diseases, including cancer invasion and metastasis [1–3]. Therefore, understanding the fundamental mechanisms of cell migration is critical for our understanding of both basic biology and the pathology of disease. Cell migration is a highly integrated multistep process that is initiated by the protrusion of the cell membrane [4]. Protrusive structures formed by migrating and invading cells were termed filopodia, lamellipodia, and invadopodia/podosomes, dependently on their morphological, structural, and functional characters (Fig. 1). Formation of these structures is driven by spatially- and temporally-regulated actin polymerization at the leading edge [5].

Cell migration and invasion are triggered by a number of chemoattractants. Upon binding to cell surface receptors, these chemoattractants stimulate intracellular signaling pathways that regulate reorganization of the actin cytoskeleton. To date, several important proteins that mediate the signaling pathways have been identified as overexpressed in several types of cancers [2] and in the subpopulation of invasive tumor cells in breast tumors [6]. Among them, Wiskott–Aldrich syndrome protein (WASP) family proteins/Arp2/3 complex, LIM-kinase/cofilin, and cortactin pathways have been studied extensively due to their apparent importance in cell migration and invasion (Fig. 2). In this review, we summarize recent findings on molecular mechanisms underlying formation of membrane protrusions and functions of these proteins particularly in cancer cell migration, invasion, and metastasis.

2. Lamellipodia generate the driving force for cell migration

Lamellipodia are flat, sheet-like membrane protrusions formed at the leading edge of migrating cells. It is generally believed that lamellipodia have a major role in driving cell migration by attaching to the substrate and generating force to

* Corresponding authors. J. Condeelis is to be contacted at tel.: +1 718 430 4669; fax: +1 718 430 8996. H. Yamaguchi, tel.: +1 718 430 3797; fax: +1 718 430 8996.
E-mail addresses: hyamaguc@aecom.yu.edu (H. Yamaguchi), condeeli@aecom.yu.edu (J. Condeelis).

0167-4889/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamcr.2006.07.001

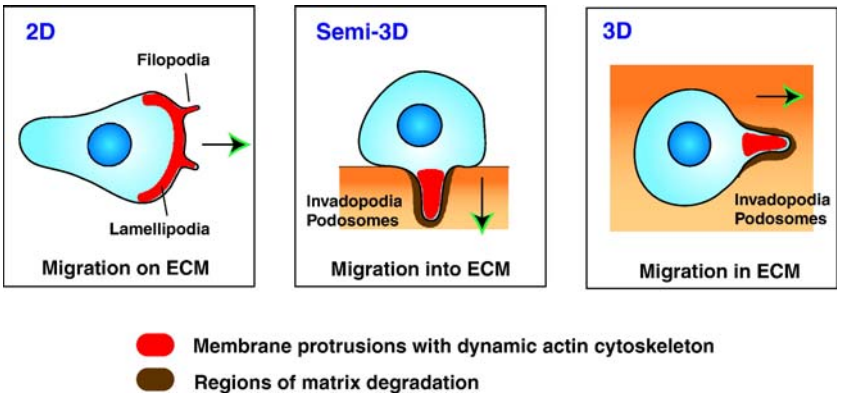

Fig. 1. Cell migration and membrane protrusions in different environments. Cells migrating on 2D substrates form membrane protrusions called filopodia and lamellipodia at the leading edge. Cells entering into and migrating in a dense rigid ECM in 3D, such as tumor cells on top of a thick ECM and those found around blood vessels, need to form membrane protrusions at the invading front, such as invadopodia and podosomes that have an ECM remodeling activity. Formation of these structures is driven by localized actin polymerization. Proteins involved in formation of these protrusions are often upregulated in malignant cancer cells and associated with increased cell motility and invasion. Arrows indicate the direction of cell migration.

pull the cell body forward. In agreement with this, carcinoma cells crawling on extracellular matrix (ECM) fibers toward blood vessels in primary tumors extend pseudopodia (functionally equivalent to lamellipodia) that attach to the fibers at the migration front [7]. Lamellipodia contain dendritic arrays of actin filaments and the molecular machinery that controls

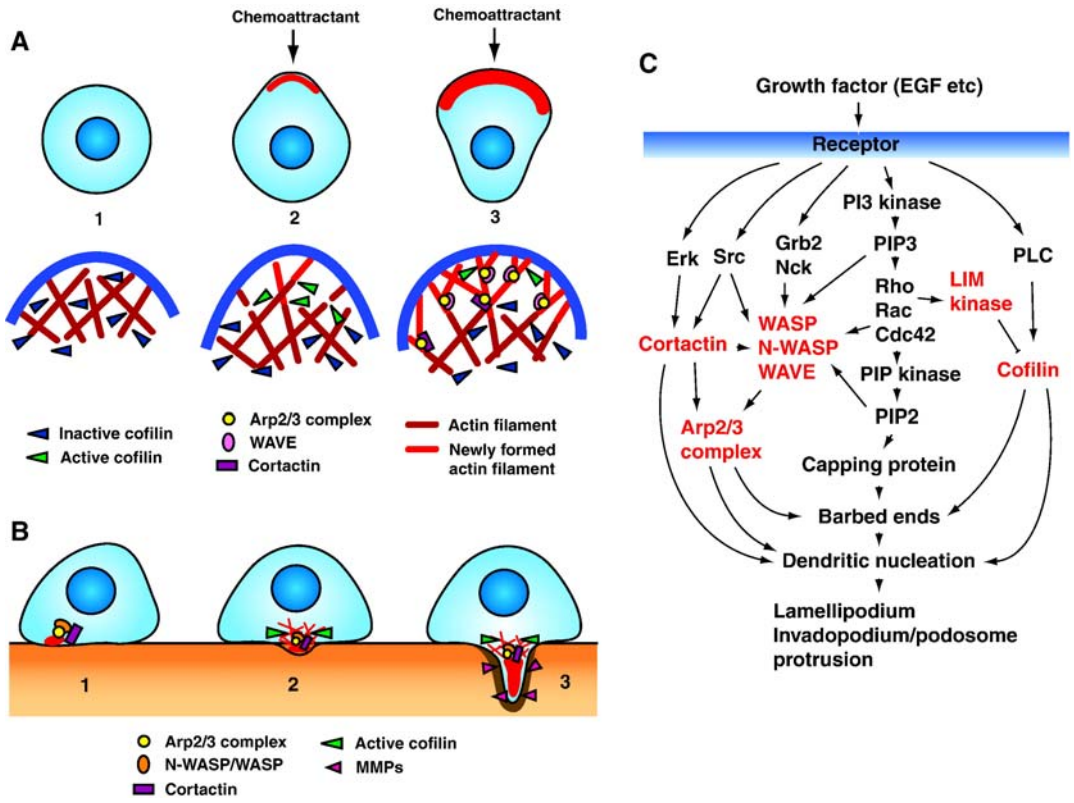

Fig. 2. Model for lamellipodium and invadopodium/podosome formation. (A) 1: Unstimulated cells have non-polarized cell morphology in which molecular machinery for barbed end formation including cofilin is inactive. 2: Chemoattractant stimulation induces local activation of cofilin at the leading edge, which leads to severing of pre-existing actin filaments and formation of free barbed ends from which new actin filaments are assembled. This initiates membrane protrusions and sets the direction of cell migration. 3: Arp2/3 complex and WAVEs associate with newly formed actin filaments and induce formation of further barbed ends and the branched actin network. Subsequently, the branched actin filaments are stabilized by cortactin. This strengthens the protrusive force of lamellipodia and leads to cell movement. (B) 1: Invadopodium/podosome formation is triggered by N-WASP/WASP, Arp2/3 complex and cortactin, probably by coupled activation of growth factor receptor and integrin signaling. 2: This precursor is stabilized by further recruitment of invadopodium/podosome components and formation of actin network by cofilin. 3: Anchored precursor then gathers matrix-degrading proteinases to degrade ECM and protrude into matrix. N-WASP/Arp2/3 complex, cortactin, and cofilin continue to induce actin polymerization to maintain the structural core. In contrast to lamellipodia, the structure and organization of actin filaments are not yet determined in invadopodia/podosomes. (C) The signaling pathways leading to protrusion of lamellipodia and invadopodia/podosomes in response to growth factor stimulation. Molecules discussed in this review are highlighted in red.