Available online at www.sciencedirect.com
ScienceDirect
J. Genet. Genomics 37 (2010) 159−172
JOURNAL OF GENETICS AND GENOMICS
www.jgenetgenomics.org

Cytokinesis and cancer: Polo loves ROCK'n' Rho(A)

Jing Li *, Jue Wang, Hong Jiao, Ji Liao, Xingzhi Xu *

Laboratory of Cancer Biology, *College of Life Science*, *Capital Normal University*, *Beijing 100048*, *China*

Received for publication 24 December 2009; revised 8 February 2010; accepted 9 February 2010

Abstract

Cytokinesis is the last step of the M (mitosis) phase, yet it is crucial for the faithful division of one cell into two. Cytokinesis failure is often associated with cancer. Cytokinesis can be morphologically divided into four steps: cleavage furrow initiation, cleavage furrow ingression, midbody formation and abscission. Molecular studies have revealed that RhoA as well as its regulators and effectors are important players to ensure a successful cytokinesis. At the same time, Polo-like kinase 1 (Plk1) is an important kinase that can target many substrates and carry out different functions during mitosis, including cytokinesis. Recent studies are beginning to unveil a closer tie between Plk1 and RhoA networks. More specifically, Plk1 phosphorylates the centralspindlin complex Cyk4 and MKLP1/CHO1, thus recruiting RhoA guanine nucleotide-exchange factor (GEF) Ect2 through its phosphopeptide-binding BRCT domains. Ect2 itself can be phosphorylated by Plk1 *in vitro*. Plk1 can also phosphorylate another GEF MyoGEF to regulate RhoA activity. Once activated, RhoA-GTP will activate downstream effectors, including ROCK1 and ROCK2. ROCK2 is among the proteins that associate with Plk1 Polo-binding domain (PBD) in a large proteomic screen, and Plk1 can phosphorylate ROCK2 *in vitro.* We review current understandings of the interplay between Plk1, RhoA proteins and other proteins (e.g., NudC, MKLP2, PRC1, CEP55) involved in cytokinesis, with particular emphasis of its clinical implications in cancer.

Keywords: Polo-like kinase 1; RhoA GTPase; Rho kinase; cytokinesis

Introduction

Cytokinesis, the last step of the M (mitosis) phase, involves physically dividing the cytoplasm of a single cell to form two daughter cells. This is a crucial step in cell cycle and has been widely studied in many model organisms: budding yeast, fission yeast, *Drosophila*, *Caenorhabditis elegans*, *Xenopus*, *Dictyostelium*, plants, and vertebrate cells (Normand and King, 2010). In animal cells the contractile ring carries out the cytokinesis step and is composed of the actin cytoskeleton and its motor molecule, myosin II (referred to as myosin in this review). But what are the regulatory proteins for the spatial and temporal events of cytokinesis? The small GTPase of Rho (Ras homologous) families are among the first proteins to be identified. Mammalian Rho GTPases comprise 20 intracellular signaling molecules, and can be subdivided into three major subsets: Rho, Rac and Cdc42 (Narumiya and Yasuda, 2006). They cycle between the inactive GDP-bound form and the active GTP-bound form. The cycling of Rho GTPases between these two states is regulated by three sets of proteins, guanine nucleotide-exchange factors (GEFs), GTPase-activating proteins (GAPs) and guanine

Abbreviation: Plk1, Polo-like kinase 1; GEF, guanine nucleotide-exchange factor; GAP, GTPase-activating protein; ROCK, Rho-associated coiled-coil-forming kinase; MLC, myosin light chain.

* Corresponding authors. Tel: +86-10-6890 9575; Fax: +86-10-6890 6307.
E-mail address: jing_li@mail.cnu.edu.cn (J. Li);
xingzhi_xu@mail.cnu.edu.cn (X. Xu)

DOI: 10.1016/S1673-8527(09)60034-5

nucleotide-dissociation inhibitors (GDIs). All three subsets of Rho GTPases are implicated in cytokinesis in different organisms, but RhoA is the most critical in mammalian cells. During cytokinesis, both induction and progression of the contractile ring depend on RhoA activation (Piekny et al., 2005).

Besides the cytoskeleton system and its interacting Rho GTPase, a successful cytokinesis also requires key protein kinases and signaling networks to coordinate the position of chromosomes in relative of the cell cortex. Cyclin-dependent kinases (Cdks), Aurora B and Polo-like kinases (Plks) are important kinases that not only regulate cytokinesis, but also are crucial regulators of other mitotic events (Glotzer, 2005; Barr and Gruneberg, 2007). There are several conserved Plks in humans, and we will only focus on Plk1 in this review, since it is believed that the major function is attributed to Plk1. Recently, some substrates of Plk1 have been identified to be involved in cytokinesis, including PRC1 (Protein Regulator of Cytokinesis 1) (Neef et al., 2007), CEP55 (CEntrosome Protein 55) (Fabbro et al., 2005), NudC (Nuclear-distribution gene C) (Zhou et al., 2003) and MKLP2 (mitotic-kinesin-like protein 2) (Neef et al., 2003). Also among these substrates are the Rho proteins: Rho GEF Ect2 (Epithelial cell transforming gene 2) (Niiya et al., 2006), Rho GAP HsCyk-4 (Burkard et al., 2009; Wolfe et al., 2009) and MKLP1/CHO1 (Liu et al., 2004). Moreover some of the RhoA downstream effectors are found to bind to the Plk1 Polo-box domain (PBD), including the Rho-associated coiled-coil-forming kinase (ROCK) (Lowery et al., 2007). ROCK is also phosphorylated by Plk1 *in vitro* (Lowery et al., 2007). Thus Plk1 and Rho GTPases are intricately linked with each other during the cytokinesis process.

It has been widely known that cytokinesis failure results in polyploidy and increased genome instability, which are frequently observed in cancer cells. In fact, Plk1, RhoA and their interacting proteins are all reported to be deregulated in some cancers. As more and more proteins involved in tumorigenesis are found to play a role in cytokinesis, such as Chk1 (Peddibhotla et al., 2009) and BRCA2 (Daniels et al., 2004), it has become apparent that cytokinesis and cancer are interconnected. This review will focus on these recent new findings in vertebrate cells and will explore its potential implication in cancer therapy, but observations from yeast and other organisms are discussed where appropriate.

The structure of Plk1 and its function in cytokinesis

Plk1 is a serine/threonine kinase that orchestrates the mitotic process. It was first discovered in *Drosophila,* as *polo* mutants fail to undergo a normal mitosis (Sunkel and Glover, 1988). And Plk1 homologues have been identified in many eukaryotes (Table 1). Plk1 has been shown to play key roles during different stages of mitosis, including mitotic entry, bipolar spindle formation, chromosome segregation and cytokinesis (Barr et al., 2004; van de Weerdt and Medema, 2006).

The structure of Plk1 is conserved across different species, with a serine/threonine kinase domain at its N-terminus and a regulatory domain, the PBD, at its C-terminus (Fig. 1A). Plk1 is activated by phosphorylation at Thr210 within the kinase domain. All Plks have a conserved PBD, and PBD has been identified as a phosphopeptide-binding motif (Elia et al., 2003). Indeed, studies

Table 1
Homologues of relevant proteins in eukaryotes

	Saccharomyces cerevisiae	*Schizosaccharomyces pombe*	*Drosophila melanogaster*	*Caenorhabditis elegans*	Mammals
Polo-like kinase 1	Cdc5	Plo1	Polo	Plc1	Plk1
Rho A	Rho1	Rho1	Rho	Rho A	Rho A
ROCK	NA	NA	Rok/Drok	LET-502	ROCK
RhoGEF/Ect2	Tom2, Tus1	NA	Pebble(Pbl)	Let-21	Ect2
GAP	NA	NA	Tumbleweed/MgcGAP50C	Cyk-4	MgcRacGAP/HsCyk-4
MKLP1	NA	NA	Pavarotti	ZEN-4	MKLP1/CHO1/Kif23
MYPT1	NA	NA	MYPT/Mbs	MEL-11	MYPT1

NA: no homologs available.