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European Journal of Cell Biology 85 (2006) 311–317
European Journal of Cell Biology
www.elsevier.de/ejcb

REVIEW

Regulation of podosomes by integrin αvβ3 and Rho GTPase-facilitated phosphoinositide signaling

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Abstract

In osteoclasts, polyphosphoinositides such as phosphatidylinositol 4,5 bisphosphate (PI(4,5)P2) and phosphatidylinositol 3,4,5 trisphosphate (PI(3,4,5)P3) are produced in response to integrin αvβ3 signaling and they have a critical role in actin cytoskeleton remodeling. The levels of PI(4,5)P2 and PI(3,4,5)P3 are regulated by Rho GTPase through the activation of phosphatidylinositol 4-phosphate 5-kinase (PI4P-5 kinase) and phospatidylinositol 3-kinase (PI3 kinase), respectively. Interaction of PI(4,5)P2 with gelsolin and Wiscott-Aldrich syndrome protein (WASP) is critical for podosome assembly/disassembly and actin ring formation in osteoclasts. Interaction of PI(3,4,5)P3 with gelsolin functions in orchestrating the podosome signaling complex consisting of several key signaling molecules. Gelsolin deficiency has been shown to block podosome assembly and motility in mouse osteoclasts. However, these osteoclasts are able to form a WASP-containing actin ring and retain their resorptive function. The TAT-mediated delivery of gelsolin phosphoinositide-binding domains into osteoclasts resulted in production of podosome clusters and disruption of actin ring formation. Hence, these osteoclasts were hypomotile and less resorptive. Our observations suggest that both PI(4,5)P2 and PI(3,4,5)P3 are involved in regulating osteoclast functions through modulation of severing, capping, and nucleating functions of actin-binding proteins.

Keywords: Osteoclasts; Integrin αvβ3; Osteopontin; Rho GTPase; Podosomes; Actin ring; Phosphoinositides; Gelsolin; WASP; PI3 kinase; PI4P-5 kinase

Contents

Abbreviations: ABPs, actin-binding proteins; HA, hemagglutinin; OPN, osteopontin; PBD, phosphoinositide-binding domain; PI(4, 5)P2, phosphatidylinositol 4, 5-bisphosphate; PI(3, 4, 5)P3, phosphatidylinositol 3, 4, 5-trisphosphate; WASP, Wiscott-Aldrich syndrome protein; PI3 kinase, phosphatidyl-inositol 3-OH kinase; PI4P-5 kinase, phosphatidyl-inositol-4-phosphate 5-OH kinase

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doi:10.1016/j.ejcb.2006.01.008

Introduction

Polyphosphoinositides (phosphatidylinositol 4,5 bisphosphate (PI(4,5)P2) and phosphatidylinositol 3,4,5 trisphosphate (PI(3,4,5)P3)) play an essential role in the regulation of actin cytoskeletal reorganization through their interaction with actin-binding proteins (ABPs). PI(4,5)P2 appears to be a general regulator of actin polymerization through its binding to several ABPs which include gelsolin, profilin, α-actinin, and vinculin (Lassing and Lindberg, 1988; Stossel, 1993; Pollard and Cooper, 1986; Fukami et al., 1994; Gilmore and Burridge, 1996). A number of phosphoinositide-binding domains (PBDs) have been identified in several cytoskeletal as well as structural proteins. Binding of phosphoinositides to these domains is highly dynamic and rapidly reversible (Zimmermann et al., 2002; Czech, 2003; Payrastre et al., 2001). This article will review and summarize some findings from our laboratory on the roles of PI(4,5)P2 and PI(3,4,5)P3 in osteoclast function. We compare our findings with that of other researchers working on similar or different cell systems.

Osteoclasts

Osteoclasts are multinucleated terminally differentiated giant cells, which play a vital role in bone resorption. Integrin $\alpha v\beta 3$ is the major functional receptor on osteoclasts. It binds to Arg-Gly-Asp (RGD)-containing extracellular matrix (ECM) proteins, such as vitronectin, osteopontin (OPN), bone sialoprotein, and a cryptic RGD site in denatured collagen (Duong and Rodan, 1998). Treatment of osteoclasts with a peptidomimetic antagonist of the $\alpha v\beta 3$ integrin, blocking antibody to $\alpha v\beta 3$ integrin, and RGD-containing peptides reduced osteoclast motility and bone resorption in vitro and in vivo (Engleman et al., 1997; Duong and Rodan, 1998; Nakamura et al., 2003). This decreased motility may be the result of a decrease in signaling by integrin $\alpha v\beta 3$ as well as of a decrease in podosome assembly/disassembly (see below). Several key molecules such as Src, PYK2/FAK, phospatidylinositol 3-kinase (PI3 kinase), p130Cas, paxillin, and Rho GTPases are implicated in the signaling mechanisms elicited by ECM/integrin interaction (Chong et al., 1994; Clark and Brugge, 1993; Erpel and Courtneidge, 1995; Worthylake and Burridge, 2001; Zhang et al., 1993). These signaling molecules are known to interact with integrin $\alpha v\beta 3$ in the podosomes of osteoclasts (Duong et al., 2000; Hruska et al., 1995; Roy et al., 2002; Saltel et al., 2004; Zhang et al., 1995).

Podosomes

Podosomes are dynamic structures present in highly motile cells. These unique cell adhesion structures are not only implicated in motility (Chellaiah et al., 2000b), but also in cell adhesion (Linder and Aepfelbacher, 2003) and matrix degradation (Delaissè et al., 2000; Goto et al., 2002). Macrophages and dendritic cells from patients with podosome-associated diseases such as Wiskott-Aldrich syndrome and chronic myeloid leukemia display deficiency in podosome formation and chemotaxis (Linder et al., 1999; Dong et al., 2003; Linder and Kopp, 2005). Osteoclasts do not express focal adhesions but use podosomes as adhesion sites. Podosomes contain many of the proteins found in focal adhesions, such as F-actin, vinculin, talin, fimbrin, gelsolin, and α-actinin (Marchisio et al., 1987; Lakkakorpi and Väänänen, 1991). Osteoclasts use the speed of assembly/disassembly of the actin cytoskeleton in the podosomes to generate high rates of motility during bone resorption (Kanehisa and Heersche, 1988; Kanehisa et al., 1990). Bone resorption is mediated by the dynamics of an actin cytoskeleton ring. Podosome assembly/disassembly and actin ring formation are directly related to structural dynamics of the actin cytoskeleton, the function of ABPs, and phosphoinositide-binding proteins (see below).

Signal transduction in response to OPN/integrin $\alpha v\beta 3$ signaling in osteoclasts

OPN is an RGD-containing ECM protein, which recognizes integrin $\alpha v\beta 3$ as a surface receptor (Chellaiah and Hruska, 1996). OPN is localized at the clear zone as well as at basolateral and ruffled border membranes of osteoclasts. OPN is deposited in the excavated lacuna during bone resorption (Chellaiah et al., 2003). Treatment of osteoclasts with OPN leads to an increase in osteoclast motility through changes in cell shape and actin cytoskeletal reorganization. The observed increase in actin assembly and F-actin content in osteoclasts is dependent on modification of PI(4,5)P2 and PI(3,4,5)P3 levels, but not on calcium fluxes (Hruska et al., 1995). The alterations in the levels of PI(4,5)P2 and PI(3,4,5)P3 in osteoclasts are due to the regulatory properties of phosphatidylinositol 4-phosphate 5-kinase (PI4P-5