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Cellular and Molecular Mechanisms of MT1-MMP-Dependent Cancer Cell Invasion

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Keywords

cancer, invadopodia, MT1-MMP, metastasis, actin, exocytosis

Abstract

Metastasis is responsible for most cancer-associated deaths. Accumulating evidence based on 3D migration models has revealed a diversity of invasive migratory schemes reflecting the plasticity of tumor cells to switch between proteolytic and nonproteolytic modes of invasion. Yet, initial stages of localized regional tumor dissemination require proteolytic remodeling of the extracellular matrix to overcome tissue barriers. Recent data indicate that surface-exposed membrane type 1–matrix metalloproteinase (MT1-MMP), belonging to a group of membrane-anchored MMPs, plays a central role in pericellular matrix degradation during basement membrane and interstitial tissue transmigration programs. In addition, a large body of work indicates that MT1-MMP is targeted to specialized actin-rich cell protrusions termed invadopodia, which are responsible for matrix degradation. This review describes the multistep assembly of actin-based invadopodia in molecular details. Mechanisms underlying MT1-MMP traffic to invadopodia through endocytosis/recycling cycles, which are key to the invasive program of carcinoma cells, are discussed.

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INTRODUCTION

The ability of cancer cells to invade tissues surrounding the primary tumor and to disseminate to distant sites is the hallmark of metastasis and a leading cause of cancer-related death (Chaffer & Weinberg 2011). Cell migration and increased capacity to overcome tissue barriers are key components of the invasive program of metastatic cells (Friedl & Wolf 2009). In preinvasive in situ epithelial carcinoma, cancer cells retain epithelial traits, including tight interactions with neighboring cells and adhesion of cells at the edge of the tumor mass with the underlying basement membrane (BM) (**Figure 1**). As the tumor progresses, cell-cell interactions loosen, and carcinoma cells adopt a fibroblast-like motile phenotype. These cells eventually breach the BM and invade through the adjacent stromal environment (Rowe & Weiss 2008).

The initial phases of tumor cell dissemination require proteolytic remodeling of the extracellular matrix (ECM) by cancer cells. Although a large body of work implicates secreted matrix metalloproteinases (MMPs) in cancer invasion (Kessenbrock et al. 2010), it has become apparent that membrane-anchored MMPs, most notably membrane type 1 (MT1)-MMP (otherwise known as MMP-14), play a key role in regional invasion in early stages of tumor progression (Hotary et al. 2003, 2006). Cancer cells adjust their levels of surface-exposed MT1-MMP, depending on the pericellular environment, and concentrate MT1-MMP at invadopodia—actin-rich ECM-degrading protrusions of cancer cells—by intracellular trafficking from internal stores. Understanding the mechanisms of invadopodia formation and spatiotemporal coordination with MT1-MMP trafficking in molecular details is important for cancer cell biology and metastasis therapeutics and is the focus of this review.

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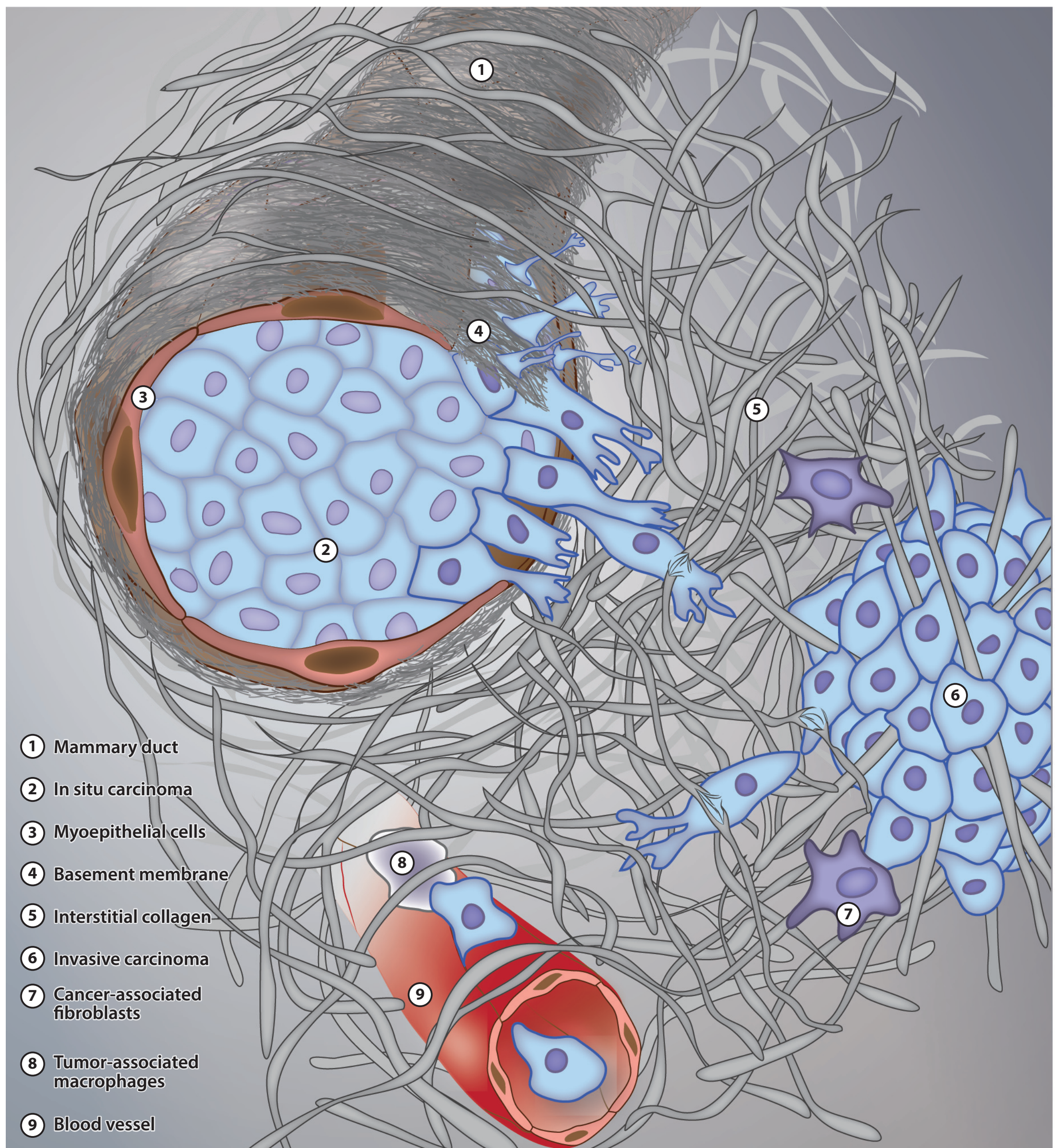

Figure 1

Simplified model depicting breast tumor progression. Schematic view of a normal duct (❶) and in situ carcinoma (❷) surrounded by myoepithelial cells (❸), which are in contact with the basement membrane (❹). Invasive cells extend invasive protrusions termed invadopodia, breach the basement membrane, invade through a fibrous interstitial collagen network in the stroma (❺), and generate invasive carcinoma (❻). In the stroma, cancer-associated fibroblasts (❼) contribute to extracellular matrix remodeling, and tumor-associated macrophages (❽) assist in intravasation of tumor cells in blood vessels (❾). Coexistence of in situ and invasive components is frequently observed in clinical specimens of breast cancer.

CANCER CELL DISSEMINATION INVOLVES PROTEASE-DEPENDENT AND PROTEASE-INDEPENDENT MECHANISMS

During metastatic dissemination, tumor cells migrate individually or as a group by using a range of mechanistically distinct modes of movement with characteristic cell morphology ranging from an elongated mesenchymal to a rounded amoeboid shape (Friedl & Alexander 2011, Lammermann & Sixt 2009). Mesenchymal migration in reconstituted three-dimensional (3D) type I collagen environment is characterized by cells with an elongated protrusion prolonging the cell body. Mesenchymal migration requires integrin-based adhesion to the matrix for traction force generation, coordinated with matrix tunnel formation on the basis of targeted proteolytic degradation of confining collagen fibrils (Fisher et al. 2009, Sabeh et al. 2009, Wolf et al. 2007, Zaman et al. 2006). In contrast, amoeboid invasive migration is characteristic of round cells with a deformable plasma membrane and high levels of actomyosin contractility and nonapoptotic blebbing activity driving forced passage through preexisting matrix pores with minimal adhesion and matrix remodeling requirements (Sahai & Marshall 2003, Sanz-Moreno et al. 2008, Tozluoglu et al. 2013, Wolf et al. 2003).

Although regulatory pathways controlling these different migratory behaviors are not fully understood, cell-autonomous factors such as a balance of Rac-driven cell protrusion and RhoA/ROCK-mediated cell contractility are critical (Sanz-Moreno et al. 2008). Environmental cues—including composition and biomechanical properties of ECM depending on meshwork size, collagen fibril alignment and cross-linking, ECM stiffness, and increased collagen deposition and cross-linking during tumor progression—also promote 3D invasive behaviors (Charras & Sahai 2014, Conklin et al. 2011, Levental et al. 2009, Pickup et al. 2014, Provenzano et al. 2008, Willis et al. 2013, Wolf et al. 2013). Possibly related to tumor cell plasticity, some degree of interconvertibility of the mesenchymal-to-amoeboid migration scheme occurs as a compensatory mode of invasion that may be activated when matrix remodeling is inhibited (Sanz-Moreno et al. 2008, Wolf et al. 2003). However, it has been argued that difficulty in reconstituting native architecture and barrier function of ECM constructs in vitro may overemphasize protease-independent invasion scenarios, questioning the physiological relevance of amoeboid motility (Demou et al. 2005, Rowe & Weiss 2008, Sabeh et al. 2009, Willis et al. 2013, Zaman et al. 2006).

MT1-MMP: THE SWORD ARM OF THE CARCINOMATOUS METASTASIS PROGRAM

BM is the first tissue barrier encountered by invasive epithelial tumor cells. It is a thin (~100–200-nm), basically two-dimensional (2D) ECM construct consisting mostly of collagen IV, laminins, nidogen, and sulfated proteoglycans, which serve as a substratum for the basal surface of epithelial cells and as a barrier that separates them from the stroma (**Figure 1**) (Kalluri 2003, Mouw et al. 2014). BM transmigration by tumor cells requires activation of a proteolytic matrix degradation program depending on proteases for execution (Bonnans et al. 2014, Rowe & Weiss 2008). Various groups of proteases are involved in ECM degradation. Such proteases include ADAMs (a disintegrin and metalloproteinases), lysosomal cathepsins, and MMPs, a group of 25 zinc-dependent endopeptidases synthesized as secreted or membrane-tethered zymogens (Bonnans et al. 2014). MT1-MMP has been identified as the main executor of the BM transmigration program of carcinoma cells in an ex vivo culture model based on native peritoneal BM (Hotary et al. 2006, Rowe & Weiss 2008). Secreted MMP-2 and MMP-9, although classified as type IV collagenases, could not endow tumor cells with native BM remodeling activity in this system (Hotary et al. 2006, Rowe & Weiss 2008). Importantly, on the basis of an intraductal xenograft model of the in

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situ–to–invasive transition of breast cancer (BC), it was recently reported that silencing of MT1-MMP in MCF10DCIS.com human breast tumor cells impaired the ability of this ductal carcinoma in situ (DCIS) tumor model to progress into infiltrating lesion (Lodillinsky et al. 2016). Thus, these data provide validation for the prominence of MT1-MMP for BM transmigration by BC cells in vivo.

Once the 2D BM has been negotiated, tumor cells invade through a 3D stromal environment (**Figure 1**, step ❺) (Yamada & Cukierman 2007). MT1-MMP has been implicated in invasive migration of mesenchymal cells through a fibrous interstitial type I collagen network, in the infiltration of vascular and lymphatic compartments, and in extravasation during metastasis (Hotary et al. 2003; Leong et al. 2014; Monteiro et al. 2013; Perentes et al. 2011; Rosse et al. 2014; Sabeh et al. 2004, 2009; Tam et al. 2002). In support of a major role during cancer dissemination, MT1-MMP is linked to malignancy of multiple tumor types—including lung, gastric, colon, breast, and cervical carcinomas, gliomas, and melanomas—and acts as the main mediator of matrix remodeling required for invasive tumor growth and metastasis (Hotary et al. 2003, 2006; Lodillinsky et al. 2016; Perentes et al. 2011; Sabeh et al. 2004; Szabova et al. 2008; Ueno et al. 1997; Zhai et al. 2005).

REGULATION OF INVADOPODIA FORMATION

ECM remodeling by cancer cells is focused in discrete pericellular zones leading to focal BM degradation and matrix tunneling (Artym et al. 2006, Fisher et al. 2009, Gligorijevic et al. 2014, Hotary et al. 2006, Schoumacher et al. 2010, Seiler et al. 2012, Wolf et al. 2007). Resulting gaps and tunnels support infiltrating cell protrusions and cell passage through the BM and invasion through the underlying fibrillar collagen microenvironment (**Figure 1**). ECM remodeling by metastatic cells is mediated by specialized cellular structures termed invadopodia, which form at the plasma membrane in association with ECM and require actin assembly for their formation (Chen 1989, Linder et al. 2011, Murphy & Courtneidge 2011). Invadopodia are the sites of surface MT1-MMP accumulation, as MT1-MMP has been identified as the main invadopodial ECM protease (Artym et al. 2006, Sakurai-Yageta et al. 2008, Steffen et al. 2008, Yu et al. 2012).

Numerous studies reported the assembly of cortactin-rich invadopodia associated with submicrometric, punctiform F-actin at the adherent plasma membranes of tumor-derived cell lines or primary tumor cells cultured atop a thin (50–100-nm) 2D layer of glutaraldehyde-cross-linked gelatin (i.e., heat-denatured collagen) (Artym et al. 2006, Clark et al. 2007). The formation of gelatin-degradative invadopodia depends on β1 integrin receptors, which are detected in their high-affinity state in punctate invadopodia in metastatic breast tumor cells and in podosome-like rosettes in Src-transformed cells (Destaing et al. 2010, Mueller et al. 1999, Sharma et al. 2013). Although the gelatin layer and BMs present some topological similarity (i.e., 2D thin substrata), in the former experimental setup, gelatin generally coats the surface of a glass coverslip, preventing extension of invasive pseudopods. When crossing native BMs or invading through stromal tissues, or when plated atop a thick ECM layer such as Matrigel (a matrix construct made of BM components), cancer cells insert invadopodia-like membrane extensions through the matrix (Gligorijevic et al. 2012, 2014; Hotary et al. 2006; Lizarraga et al. 2009; Schoumacher et al. 2010).

Punctate invadopodia abundantly form on the basis of α2β1 integrin receptors at the adherent surface of carcinoma cells plated on a high-density, high-concentration fibrillar collagen network or decellularized tumor tissues mimicking the dense stromal cancer microenvironment (Artym et al. 2015). When embedded within (or plated atop) a 3D fibrous type I collagen network, tumor cells assemble elongated (from 0.5 μm up to several micrometers long) invadopodia (termed linear invadopodia) aligned with collagen fibrils contacting the opposite side of the plasma membrane and

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involved in remodeling of confining fibrils (Juin et al. 2012, Monteiro et al. 2013, Wolf et al. 2007). Integrin receptors do not seem to play a role in linear invadopodia formation. Rather, this process involves the collagenic DDR1 receptor in human MDA-MB-231 mammary adenocarcinoma cells (Juin et al. 2012, Juin et al. 2014). Thus, invadopodia formation appears to be directed by the interaction of ECM components with the repertoire of cell-matrix adhesion receptors expressed by cancer cells, which, depending on ECM composition, microarchitecture, and biomechanics, determine the organizational architecture of invadopodia (Alexander et al. 2008; Artym et al. 2015; Destaing et al. 2010, 2011; Juin et al. 2014; Parekh et al. 2011).

Growth factors also induce invadopodia formation in cancer cells, possibly acting in combination with adhesion cues and underscoring the importance of cross talk between adhesion and growth factor receptor signaling for cancer invasion (Hoshino et al. 2013a). Epidermal growth factor (EGF) (Mader et al. 2011, Yamaguchi et al. 2005), transforming growth factor β (TGFβ) (Pignatelli et al. 2012), and hepatocyte growth factor (HGF) (Rajadurai et al. 2012) can induce or increase invadopodia formation in cancer cells. Protein tyrosine kinase c-Src, phosphoinositide 3-kinases (PI3Ks), and Rho GTPases act as common signaling nodes mediating invadopodia formation in response to activating signals from these various adhesion and growth factor receptors (Beaty & Condeelis 2014, Hoshino et al. 2012a, Murphy & Courtneidge 2011).

MULTISTEP INVADOPODIUM ASSEMBLY

Studies using tumor cells plated on a thin layer of gelatin revealed that invadopodia formation is a multistage process initiated by the assembly of F-actin, cortactin-positive invadopodia precursor elements (Albiges-Rizo et al. 2009, Beaty & Condeelis 2014, Linder et al. 2011, Murphy & Courtneidge 2011). Precursors are progressively stabilized and gain matrix degradative capacity as MT1-MMP accumulates during invadopodia maturation (Artym et al. 2006, Branch et al. 2012, Mader et al. 2011, Oser et al. 2009, Sharma et al. 2013).

Cdc42/N-WASP/Arp2/3 Actin Assembly Module

Assembly of invadopodial actin core structures requires activation of the Arp2/3 complex by Cdc42 Rho GTPase acting upstream of neuronal Wiskott–Aldrich syndrome protein (N-WASP); thus, the core actin invadopodium framework comprises a branched actin filament network (Beaty & Condeelis 2014; Desmarais et al. 2009; Juin et al. 2012, 2014; Monteiro et al. 2013; Yamaguchi et al. 2005; Yu et al. 2012). Using an orthotopic mammary allograft tumor model, investigators observed that N-WASP silencing reduced the formation of invadopodial membrane protrusions and decreased invasion, intravasation, and lung metastasis in vivo (Gligorijevic et al. 2012). The Cdc42/N-WASP/Arp2/3 complex actin assembly module has been implicated in the formation of invadopodia-related podosomes required for tissue infiltration by cells of the innate immune response, in endothelial cells during blood vessel remodeling, and in the formation of invadopodia-like structures in anchor cells during vulval development in *Caenorhabditis elegans* (Linder et al. 2011, Lohmer et al. 2016, Varon et al. 2006). This module, representing an evolutionarily conserved mechanistic feature of podosome assembly schemes for developmental invasion programs and tissue homeostasis, is hijacked for invadopodia assembly by metastatic cells. Actin nucleators of the Diaphanous-related formin (DRF) family also contribute to invadopodia function (Kim et al. 2016, Lizarraga et al. 2009). Generation of parallel filament arrays by DRFs may contribute to invadopodia elongation and extension deeper into the substratum, which may be associated with invadopodia maturation (Schoumacher et al. 2010). In addition, regulators of actin filament turnover and bundling such as cortactin, cofilin, and fascin are critically involved in coordinating

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invadopodia assembly and membrane protrusion formation and control invasiveness (Desmarais et al. 2009, Li et al. 2010, Magalhaes et al. 2011, Oser et al. 2009, Razidlo et al. 2014, Yamaguchi et al. 2005).

Cortactin in Invadopodia Formation

F-actin binding and the actin branch–stabilizing protein cortactin are critical for invadopodia formation and are widely used as an invadopodia marker (Artym et al. 2006, Ayala et al. 2008, Bowden et al. 1999, Clark et al. 2007). Concerted EGF- and c-Src-dependent coactivatory phosphorylation events and interaction of β1 integrin cytoplasmic tail with Arg Abl-family nonreceptor tyrosine kinase lead to Arg-dependent phosphorylation of cortactin on tyrosine 421 (Y^{421}) (Beaty et al. 2013, Mader et al. 2011). Phosphorylation of cortactin Y^{421} is a key switch triggering recruitment of Nck1 adaptor protein, N-WASP, and cofilin in invadopodia (Oser et al. 2009, 2010). Increased barbed-end formation and actin filament turnover by cofilin together with N-WASP/Arp2/3 complex activation enhance actin assembly and membrane protrusion responses (Magalhaes et al. 2011). In agreement with a promoting role in tumor cell invasiveness, upregulation and dysfunction of cortactin, including deregulation of phosphorylation and acetylation state, have been implicated in cancer progression and metastasis (Buday & Downward 2007, Castro-Castro et al. 2012, Rey et al. 2011, Weaver 2008, Zhang et al. 2007, Zhang et al. 2009).

An additional consequence of tyrosine phosphorylation of cortactin is the recruitment of sodium hydrogen exchanger NHE1, a transmembrane protein exchanging extracellular sodium for intracellular protons across the invadopodial plasma membrane (Magalhaes et al. 2011). A local increase in intracellular pH due to NHE1 activity disrupted an inhibitory cortactin/cofilin complex, promoting the generation of fast-growing actin filament barbed ends and actin filament turnover by free cofilin (Magalhaes et al. 2011). Concomitant acidification of the peri-invadopodial space may favor ECM proteolysis by secreted acidic cathepsins, consistent with studies implicating these enzymes during BM invasion programs (Busco et al. 2010, Rothberg et al. 2013, Webb et al. 2011). Acidification of the pericellular microenvironment may be further enhanced by voltage-gated Na^+ channel $Na_V1.5$, which interacts with and activates NHE1 and is found in invadopodia in invasive MDA-MB-231 BC cells (Brisson et al. 2013, Gillet et al. 2009). However, inhibitors of cathepsins failed to suppress remodeling of native peritoneal BM by carcinoma cells, arguing against a significant role for peritumoral acidification in BM remodeling (Hotary et al. 2006).

Tks4/Tks5 and ROS Production

Although the complete sequence of events involved in invadopodia maturation is unknown, recruitment of phox homology (PX) domain–containing Tks5/FISH- and Tks4-related proteins (SH3PXD2A and -B) coordinated with PI3K signaling seems to be crucial, as these events are associated with maturation of short-lived ($\leq$10-min) actin-based precursors into stable ($\geq$60-min), proteolytically active invadopodia (Diaz & Courtneidge 2012, Hoshino et al. 2012a, Seals et al. 2005, Sharma et al. 2013, Yamaguchi et al. 2011). c-Src substrate proteins Tks4 and Tks5 (Seals et al. 2005), which are the most exclusive invadopodial markers identified so far, harbor multiple SH3 domains, polyproline-rich motifs, and a PX domain, which binds membrane phosphoinositides PI(3)P and PI(3,4)P_2 (Abram et al. 2003). Tks5 interacts with N-WASP through its SH3 domain, and c-Src-phosphorylated Tks5 interacts with Nck, linking Tks5 to invadopodial F-actin assembly and ECM degradation (Eckert et al. 2011, Oikawa et al. 2008, Seals et al. 2005, Stylli et al. 2009). In addition, inhibition of invadopodia formation upon knockdown of Tks5 correlates with a strong reduction of lung metastasis in a mouse tumor model in vivo (Eckert et al. 2011).

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Intriguingly, the multidomain architecture of Tks proteins is related to that of $p47^{Phox}$/NOXO2 protein (SH3PXD1A), which serves as an organizer subunit of NADPH oxidase (NOX), the multicomponent enzymatic complex that generates reactive oxygen species (ROS) (Diaz et al. 2009, Gianni et al. 2009). Along this line, Tks4 and -5 act as organizer subunits, allowing for NOX1- and NOX3-dependent ROS generation. ROS production is required for the formation and stability of Tks-dependent invadopodia, as revealed by inhibition of invadopodia formation by ROS scavenger *N*-acetyl cysteine and NOX inhibitor diphenyleneiodonium chloride (Diaz et al. 2009, Gianni et al. 2009). However, it remains unknown whether and how Tks4/5 and possibly ROS can influence acquisition of proteolytic function by mature invadopodia. Another pathway potentially linking ROS production to invadopodial actin assembly and invasiveness of BC cells involves upregulation of NOX4 gene expression upon loss of the tumor suppressor $TIS21^{/BTG2/Pc3}$ in BC cell lines; such upregulation leads to derepression of a DRF-family actin nucleator and to stimulation of invadopodial actin polymerization (Choi & Lim 2013, Choi et al. 2016).

In the invadopodium model of cancer cell invasion, actin polymerization is instrumental in driving pseudopodial cell protrusion and insertion through the matrix as a means of maintaining tight apposition of MT1-MMP-based pericellular proteolytic machinery with ECM substrates. In addition, binding of the 20-amino-acid-long MT1-MMP cytosolic tail to the underlying F-actin network is thought to anchor MT1-MMP to the invadopodial plasma membrane (Yu et al. 2012). In this model, invadopodia are considered to be MT1-MMP-receiving platforms. Who makes the call for MT1-MMP delivery, and which carrier(s) conveys MT1-MMP cargo to invadopodia? What are the routes and regulators of MT1-MMP traffic to invadopodia? These questions are addressed in the following sections.

REGULATION OF MT1-MMP SURFACE LEVELS

MT1-MMP, a type I transmembrane protein produced as a latent ~72-kDa zymogen, is processed by furin-like proprotein convertases into an ~60-kDa catalytically active protease during its transit to the plasma membrane (Yana & Weiss 2000). From the cell surface, MT1-MMP is rapidly internalized by clathrin-mediated endocytosis on the basis of a dileucine ($L^{571}L^{572}$) motif in its cytoplasmic tail, which mediates binding to clathrin adaptor complex AP-2 (see Poincloux et al. 2009 and references herein). Accordingly, surface expression of MT1-MMP is generally low, and upregulation correlates with malignancy in cancer (Lodillinsky et al. 2016, Marchesin et al. 2015, Rosse et al. 2014).

Several mechanisms contribute to regulation of MT1-MMP endocytic rates in cancer cells. Endocytic clearance of surface MT1-MMP requires Endophilin A2 (EndoA2), which acts together with dynamin-2 to promote fission of endocytic carriers from the plasma membrane (Wu et al. 2005). A regulatory loop implicating c-Src-mediated phosphorylation of EndoA2 Y^{315} depending on the scaffolding function of focal adhesion kinase inhibits MT1-MMP endocytosis by disrupting EndoA2/dynamin-2 interaction (Wu et al. 2005). Blunting the endocytic function of EndoA2 promotes invasive potential and metastasis (Fan et al. 2013, Wu et al. 2005). However, a recent study reported that silencing of EndoA2 impairs ECM degradation and MT1-MMP internalization in triple-negative BCs (TNBCs) (highly aggressive breast tumors negative for estrogen receptor, progesterone receptor, and HER2), whereas elevated EndoA2 levels increase malignancy and result in a poor prognosis in TNBCs (Baldassarre et al. 2015). Reduction of invasive potential upon EndoA2 knockdown has been attributed to the reduction of internalized pools of MT1-MMP, preventing efficient recycling to invadopodia from intracellular storage compartments (Baldassarre et al. 2015).

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Caveolae may contribute to MT1-MMP internalization in fibrosarcoma and glioma cells on the basis of cell fractionation and global alterations in membrane cholesterol levels (Annabi et al. 2004, Remacle et al. 2003). Along this line, silencing of the main caveolae component, caveolin-1, interfered with MT1-MMP-dependent ECM degradation in MDA-MB-231 BC cells (Yamaguchi et al. 2009). However, a direct role for caveolae in cargo uptake has been long debated, and more specific caveolar functions should be envisaged, such as roles in signal transduction, lipid signaling, and plasma membrane resistance to mechanical stress, which may be more relevant in the contexts of MT1-MMP and invadopodia-dependent functions in tumor invasion (Cheng & Nichols 2016, Goetz et al. 2011, Parton & del Pozo 2013, Yang et al. 2016).

We are faced with a seeming paradox: MT1-MMP is efficiently cleared from the cell surface by endocytosis, but its function in ECM remodeling requires some stable association with the invadopodial plasma membrane. An explanation came from fluorescence recovery after photobleaching (FRAP) analysis that revealed differential limited mobility of MT1-MMP in invadopodial domains of the plasma membrane, contrasting with high dynamics and high internalization rates in noninvadopodial plasma membrane regions (Hoshino et al. 2012b, Yu et al. 2012). Anchoring of the cytoplasmic tail of MT1-MMP to the invadopodial F-actin network is a component of a stabilization mechanism because deletion of the MT1-MMP cytosolic tail or silencing of N-WASP restores high-mobility behavior (Yu et al. 2012). Inhibition of MT1-MMP clearance by interaction with fibrillar collagen in the tumor microenvironment may represent an additional mechanism by which to increase surface levels of active protease at invadopodia (Lafleur et al. 2006).

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MECHANISM OF POLARIZED MT1-MMP TRAFFIC TO INVADOPODIA

Recycling of Internalized MT1-MMP Occurs from Late Endosomes/Lysosomes

Delivery of MT1-MMP to invadopodia is critical for their formation and functionality, and understanding the routes and mechanisms of polarized MT1-MMP trafficking in invasive cancer cells is of paramount interest. In contrast to the assumption that invadopodial delivery of MT1-MMP is mediated by trafficking through the biosynthetic pathway (i.e., ER to Golgi to plasma membrane), data support the idea that MT1-MMP is first internalized and then rerouted to invadopodia from endocytic compartments. Endocytic/exocytic fluxes are thought to be essential to ensure a constant flow of active MT1-MMP at the plasma membrane, where its proteolytic activity becomes rapidly inactivated by binding to tissue inhibitor of metalloproteases-2, which is abundantly expressed in cancer (Zhu et al. 2015). Convergent observations in several carcinoma cell lines have identified a recycling pathway involving Rab7-, VAMP7-positive late endosomes (LEs)/lysosomes in returning internalized MT1-MMP to the invadopodial plasma membrane (Chevalier et al. 2016, Hoshino et al. 2013b, Macpherson et al. 2014, Monteiro et al. 2013, Rosse et al. 2014, Steffen et al. 2008, Williams & Coppolino 2011, Yu et al. 2012). The relevance of this recycling circuitry was recently established in the context of the invasive program of BC (Chevalier et al. 2016, Macpherson et al. 2014, Marchesin et al. 2015, Rosse et al. 2014). An early study identified Rab8 GTPase as a regulatory component of an exocytosis pathway of MT1-MMP to invasive plasma membrane protrusions in MDA-MB-231 BC cells (Bravo-Cordero et al. 2007). Other studies found that Rab8 deregulation in carcinoma causes LE/lysosomal mislocalization of apical proteins and loss of epithelial polarity associated with a mesenchymal invasive program (Chou et al. 2016, Sato et al. 2007). An endocytic/exocytic cycle of MT1-MMP based on Rab5A and Rab4 GTPases has been identified. This pathway is associated with metastatic dissemination of estrogen receptor–positive BCs, indicating that different circuitries may operate, depending on tumor molecular context (Frittoli et al. 2014).

WASH-Dependent Actin Assembly Occurs on MT1-MMP-Containing Endosomes

A comprehensive model has emerged from analysis of MT1-MMP recycling from LE/lysosomal compartments in TNBCs (see **Figure 2**). A characteristic trait is the presence of discrete submicrometric actin dots on MT1-MMP-positive LEs/lysosomes, which contain and depend on the Arp2/3 complex, its upstream activator (WASP family member WASH), and cortactin for their formation (**Figure 2**) (Monteiro et al. 2013, Rosse et al. 2014). Silencing of WASH in TNBC cells inhibits endosomal actin dots and MT1-MMP delivery to invadopodia and interferes with pericellular matrix degradation and cell invasion (Monteiro et al. 2013). Endosomal actin dots are regulated by atypical protein kinase C iota (aPKCι) through cortactin phosphorylation, and silencing of aPKCι leads to actin dot enlargement, probably through deregulation of endosomal actin dynamics, and affects MT1-MMP trafficking to invadopodia and invasion in TNBCs (Rosse et al. 2014). Co-upregulation of oncogenic aPKCι and MT1-MMP has been found in hormone receptor–negative BCs and correlates with malignancy and poor prognosis (Rosse et al. 2014).

Multiprotein WASH complex and actin dots are present on endosomal compartments in different cell types, and although not fully understood, their function is related to endosomal membrane tubulation in connection with cargo sorting and generation of transport intermediates (Derivery et al. 2012, Gomez & Billadeau 2009, Gomez et al. 2012, Puthenveedu et al. 2010, Zech et al. 2011). Endosomal recruitment of WASH is mediated by the retromer, a multiprotein complex involved in endosomal cargo sorting and transport, and retromer association with LEs is controlled by Rab7 (Harbour et al. 2010). Rab7 has been shown to regulate MT1-MMP trafficking to invadopodia (Williams & Coppolino 2011), although retromer function has not been investigated. Recent studies have identified interactions of WASH with several subunits of the octameric exocyst complex, and silencing of WASH impaired recruitment of the exocyst complex and of c-Jun N-terminal kinase (JNK)-interacting proteins 3 and 4 (JIP3 and JIP4) on MT1-MMP-containing LEs/lysosomes (Marchesin et al. 2015, Monteiro et al. 2013). Alteration of these key membrane traffic regulators, which colocalize with WASH/actin/cortactin-positive puncta, impairs MT1-MMP trafficking and invadopodia-mediated TNBC cell invasiveness (Liu et al. 2009, Marchesin et al. 2015, Monteiro et al. 2013, Sakurai-Yageta et al. 2008). Together, these findings identify WASH as a critical hub for functional endosomal membrane subdomain organization.

Endosomal Membrane Tubules Mediate MT1-MMP Delivery to Invadopodia

JIP3 (with splice variants MAPK8IP3 and JSAP1) and JIP4 (with splice variants SPAG9 and JLP) are related scaffolding proteins involved in JNK and p38 signaling modules, respectively (Ito et al.

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Figure 2

Delivery of MT1-MMP to the invadopodial membrane is a complex, multistep process requiring microtubule-based transport. (*a*) Hypothetical model depicting MT1-MMP transport to invadopodia. MT1-MMP-containing late endosomes (❶) are transported along microtubules by dynein and kinesin motors. Association of dynein/dynactin minus (−) end–directed motor with kinesin-1 plus (+) end–directed motor requires the JIP3 and JIP4 proteins. Kinesin-2 association is independent of JIPs. The endosomal association of JIP3 and JIP4 depends on WASH, which is responsible for assembly of the endosomal actin network through activation of the Arp2/3 complex. At the cell periphery, active GTP-bound ARF6 and JIP3 and JIP4 mediate a kinesin-1 and dynactin/dynein tug-of-war, leading to MT1-MMP endosomal tubulation and delivery of MT1-MMP to the invadopodial plasma membrane (❷) at plasma membrane/extracellular matrix (ECM) contact sites. GTP hydrolysis on ARF6 releases the dynein/dynactin brake, and dynamin-2 catalyzes the fission of the endosome–to–plasma membrane tubular connection, allowing for clearance of MT1-MMP-positive endosomes from the cell periphery (❸). (*b*) Images of MT1-MMP-containing endosomes (*magenta*) with associated JIP4 (*orange*) and cortactin (*green*) proteins. The right subpanel is a 3D Imaris reconstruction of endosomes shown in the left subpanel.

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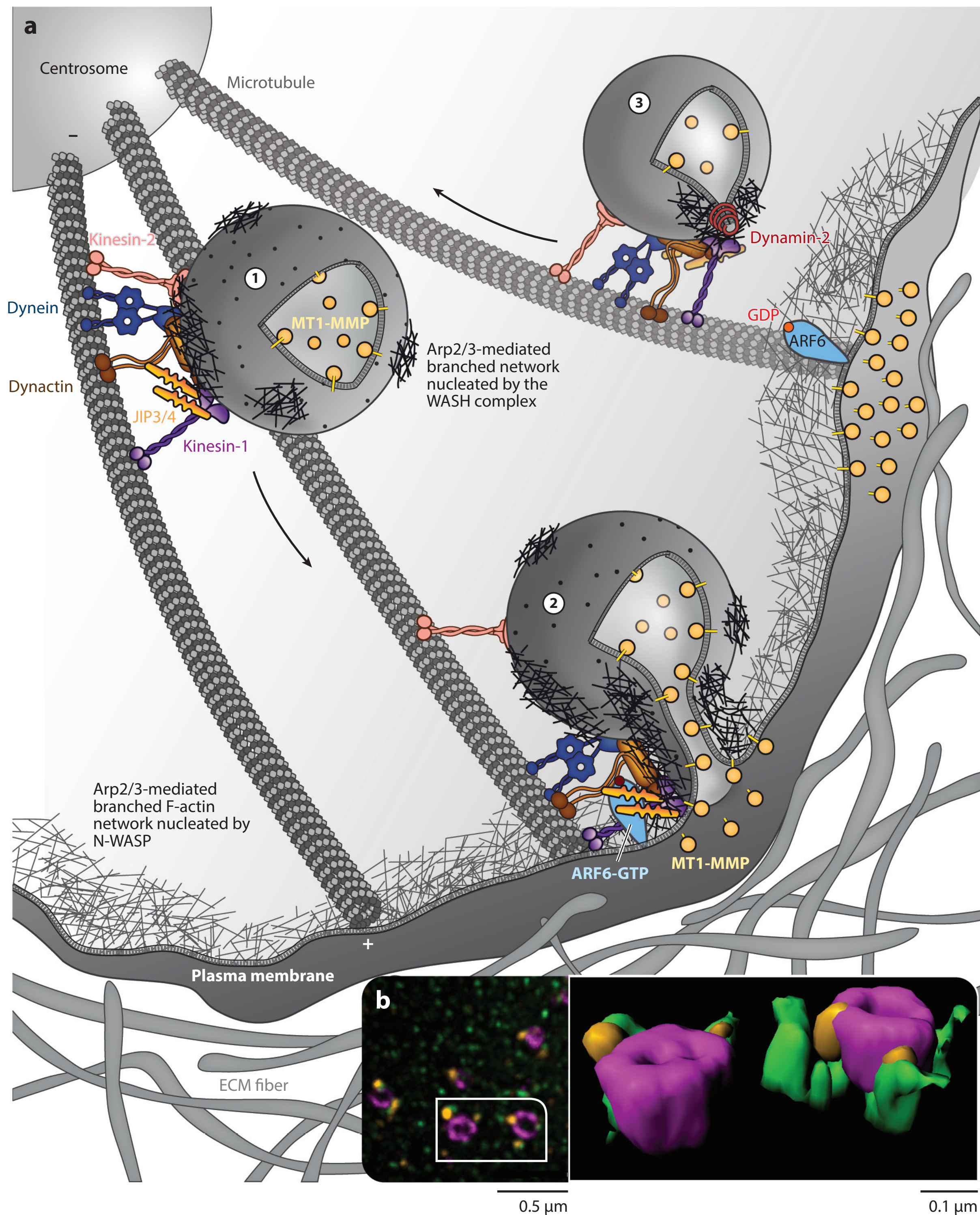

1999, Kelkar et al. 2005). JIP3 mRNA levels are significantly upregulated in highly aggressive glioblastoma tumors (Takino et al. 2005), whereas mRNA and protein levels of SPAG9 are elevated in a variety of human cancers, including renal, breast, cervical, prostate, colon, and lung carcinomas (Garg et al. 2007, 2008; Jilg et al. 2014; Kanojia et al. 2009, 2011). In addition, JIP3 and JIP4 associate with both plus end–directed kinesin-1 and minus end dynein/dynactin motors and control microtubule-based motility and directionality of vesicle movement during axonal transport in neurons (Bowman et al. 2000, Cavalli et al. 2005). JIP3 and JIP4 are required for kinesin-1 and dynein/dynactin association with MT1-MMP-positive endosomes in MDA-MB-231 cells, whereas kinesin-2 recruitment occurs independently of JIPs (**Figure 2**, step ❶) (Marchesin et al. 2015). Lack of any of these motors altered microtubule-based motility of MT1-MMP-positive endosomes and affected invadopodial function (Marchesin et al. 2015). Kinesin-1 and -2 have similarly been implicated in vesicular transport of MT1-MMP to macrophage podosomes (Wiesner et al. 2010). Previous work in breast tumor cells revealed that MT1-MMP-containing endosomes are polarized toward the plasma membrane in association with ECM fibers and are docked at invadopodia (Monteiro et al. 2013). MT1-MMP exocytosis may involve the formation of endosomal tubular connections between docked endosomes and the invadopodial plasma membrane (Monteiro et al. 2013, Steffen et al. 2008). Formation of endosomal tubules mediating MT1-MMP transfer to the surface required the JIP3 and JIP4 proteins and their upstream regulator ARF6 (Marchesin et al. 2015). The small GTP-binding protein ARF6 is frequently overexpressed in cancer, and its expression levels correlate with tumor invasion and metastasis (D'Souza-Schorey & Chavrier 2006, Hashimoto et al. 2004, Muralidharan-Chari et al. 2009). In BC cells, ARF6 is activated by EGF receptor (EGFR) via its guanine exchange factor, GEP100/BRAG2 (Morishige et al. 2008, Sabe et al. 2009). ARF6 regulates JIP3 and JIP4's interaction with dynein/dynactin and kinesin-1 motors (Marchesin et al. 2015, Montagnac et al. 2009, Suzuki et al. 2010). A mechanism has been proposed whereby active GTP-bound ARF6 in the invadopodial plasma membrane grabs dynein/dynactin anchored in place on microtubules through its effectors, JIP3 and JIP4. As dynein/dynactin and kinesin-1 are motors with opposite directionality, anchored endosomes become partially tubulated (**Figure 2**, step ❷) (Marchesin et al. 2015). This microtubule, dynein/dynactin, and kinesin-1 tug-of-war mechanism is also supported by the observation that mature invadopodia contain microtubules (Schoumacher et al. 2010). In addition, immunohistochemistry analysis of a BC tissue microarray has shown that the ARF6/kinesin-1/MT1-MMP axis is overexpressed in high-grade TNBCs (Marchesin et al. 2015). Finally, WASH also contributes to endosomal tubulation and MT1-MMP transfer to the surface (Marchesin et al. 2015, Monteiro et al. 2013), illustrating the coordination between actin-driven endosomal membrane deformation and tubular extension, depending on the dynein/dynactin and kinesin-1 tug-of-war mechanism.

Dynamic Interactions of MT1-MMP-Containing Late Endosomes/Lysosomes with Invadopodia

In a last step, MT1-MMP-positive endosomes, which remain anchored to invadopodia for several minutes and do not collapse in the plasma membrane (Monteiro et al. 2013), detach and clear off, depending on dynein/dynactin minus end–directed motor function (**Figure 2**, step ❸) (Marchesin et al. 2015). Of note, ARF6 knockdown in MDA-MB-231 cells triggers a drastic accumulation of MT1-MMP-positive endosomes in the perinuclear cell region as a result of unbalanced dynein/dynactin activity (Marchesin et al. 2015). Thus, it can be postulated that the duration of MT1-MMP-containing LE/lysosome docking to the plasma membrane is controlled by ARF6 deactivation after GTP hydrolysis to unleash dynein/dynactin by releasing the interaction of ARF6 and JIPs (**Figure 2**, step ❸). In addition, invadopodia function requires the activity of

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dynamin-2, which associates with actin on MT1-MMP-containing endosomes and invadopodia and may be involved in endosomal detachment by promoting the fission of endosome/plasma membrane tubular connection (Baldassarre et al. 2003, Rosse et al. 2014). Docking/detachment cycles are thought to provide MT1-MMP-containing endosomes with the necessary dynamic behavior to support invasive cancer cell plasticity and adaptation to changing ECM microenvironments.

Other regulators of MT1-MMP exocytosis and membrane docking have been identified. One such example is the exocyst complex, a hetero-octameric complex proposed to tether exocytic vesicles to the plasma membrane before SNARE-mediated fusion (Heider & Munson 2012). In MDA-MB-231 BC cells, the exocyst complex is required for invadopodia function in matrix degradation by controlling MT1-MMP exocytosis (Liu et al. 2009, Sakurai-Yageta et al. 2008). Exocyst interacts with the endosomal WASH complex on MT1-MMP-positive LEs/lysosomes, whereas its association with invadopodia involves binding to Cdc42 and/or RhoA, thus bridging WASH/exocyst endosomal membrane subdomains with the invadopodial plasma membrane (Monteiro et al. 2013, Sakurai-Yageta et al. 2008). In addition, phosphorylation of the Exo70 exocyst subunit by ERK1/2 in response to EGF promotes Exo70 incorporation into the exocyst complex and is required for invadopodia activity, thus linking EGFR signaling with invadopodia function (Ren & Guo 2012). Studies also identified VAMP7 as the LE/lysosomal SNARE protein involved in MT1-MMP traffic to invadopodia (Steffen et al. 2008, Williams & Coppolino 2011). A VAMP7/syntaxin4/SNAP23 association with invadopodia, which is responsible for MT1-MMP delivery, was recently reported (Williams et al. 2014). These findings define VAMP7 together with syntaxin4 and SNAP23 as the cognate SNAREs responsible for MT1-MMP recycling from LE/lysosomal stores, probably by facilitating fusion of MT1-MMP vesicular/tubular carriers with the invadopodial plasma membrane. Data also support a mechanism whereby the aforementioned interactions of LE/lysosomal organelles with invadopodia may promote the secretion of an exosomal pool of active MT1-MMP in the extracellular space (Hoshino et al. 2013b). Exosomes correspond to 50–100-nm vesicles generated intracellularly by inward budding from the limiting membranes of LEs/lysosomes to produce multivesicular bodies (MVBs) and released upon MVB fusion with the plasma membrane (Colombo et al. 2014). A fraction of MT1-MMP is present in intraluminal vesicles in MVBs and may be directed to exosomes for extracellular release by fibrosarcoma and melanoma cells (Hakulinen et al. 2008, Rosse et al. 2014). Release of MT1-MMP-positive exosomes occurs at invadopodia in invasive head and neck squamous cell carcinoma cells and requires the small GTPase Rab27A (Hoshino et al. 2013b). The contribution of an exosomal pool of MT1-MMP to ECM invasion program of cancer cells is not known; extension of the perimeter of MT1-MMP action compared with the case of a conventional invadopodia-based ECM remodeling model is anticipated. However, besides the function of Rab27A in exosomal secretion (Bobrie et al. 2012, Ostrowski et al. 2010), its role in transport of MT1-MMP-containing LEs/lysosomes to cell/matrix contact sites and to endosome–to–plasma membrane transfer of MT1-MMP related to canonical invadopodia function should not be excluded (Macpherson et al. 2014).

CONCLUSION AND FUTURE LINES OF RESEARCH

How the different players involved in MT1-MMP exocytosis are organized in time and space to ensure coordinated delivery of MT1-MMP to invadopodia is not precisely known. The function of the exocyst complex in MT1-MMP recycling to invadopodia requires localized Cdc42 and/or RhoA activation, promoting recruitment of the exocyst complex to invadopodia-associated IQGAP1 (Sakurai-Yageta et al. 2008). IQGAP1, which has been implicated in tumorigenesis and

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invasive migration (White et al. 2009), associates with and regulates the activity and signaling of multiple small GTPases (Jacquemet & Humphries 2013). Cdc42 is central to the mechanism of invadopodia formation (Hoshino et al. 2012a, Juin et al. 2014, Razidlo et al. 2014, Sakurai-Yageta et al. 2008, Yamaguchi et al. 2005). IQGAP1, which prolongs Cdc42 activation (Smith et al. 2015), may thus control invadopodium lifetime through Cdc42. IQGAP1 also copurifies with ARF6, and the molecular consequences of this interaction should be explored (Ewing et al. 2007, Hu et al. 2009). Cancer cells invading through 3D ECM networks must adapt to a changing ECM environment and degrade new confining fibers as they migrate. The ARF6 GTP/GDP cycle is thought to control the sequence of MT1-MMP/endosomal docking/detachment from the plasma membrane, coordinated with the invadopodium assembly/disassembly cycle necessary for productive invasive migration (Marchesin et al. 2015). Noticeably, a proinvasive, prometastatic potential of the NEDD9 scaffolding protein has been related to its capacity to control recycling of MT1-MMP from LEs/lysosomes by promoting GTP hydrolysis on ARF6 through interaction with ARAP3 GTPase-activating protein (ARF6-GAP) at invadopodia (Loskutov et al. 2015). Molecular players, including the NEDD9/ARAP3 association or other ARF6-GAPs that contribute to dynamic interactions of MT1-MMP-positive endosomes with invadopodia, should be identified.

In addition, IQGAP1, which interacts with actin filaments and regulates actin assembly, associates with several microtubule plus end tracking proteins (Abel et al. 2015 and references herein). Microtubule-based, bidirectional movement of fluorescently labeled, MT1-MMP-containing vesicles can be observed by live-cell imaging in different cancer cells. MT1-MMP recycling may be favored by anchoring microtubule plus ends to the cortical invadopodial actin meshwork, a prediction that should be tested. Furthermore, polarized movement of MT1-MMP transport carriers toward microtubule plus ends is likely actively regulated in response to invadopodium assembly stimuli (Macpherson et al. 2014, Marchesin et al. 2015, Monteiro et al. 2013, Yu et al. 2012). Several observations suggest that JIP3 and JIP4 and their nonmammalian orthologs can signal changes in cargo direction through physical interaction with kinesin-1 and dynein/dynactin motors (Abe et al. 2009, Arimoto et al. 2011, Cavalli et al. 2005, Montagnac et al. 2009, Sun et al. 2011). JIP3 also interacts with and mediates activation of JNK, and activated JNK has been colocalized with dynactin complex components (Cavalli et al. 2005, Drerup & Nechiporuk 2013). A testable prediction is that JNK proinvasive signals acting through elevated JIP3/4 levels in carcinoma cells may control the directionality of MT1-MMP-positive vesicle movement toward the invasive plasma membrane. Moreover, trafficking of MT1-MMP is strongly dependent on aPKCι in TNBCs (Rosse et al. 2014). Increased expression of aPKCι during epithelial cancer progression is associated with disruption of epithelial polarity. More generally, how epithelial polarity factors are diverted from their normal functions and contribute to the invasive capacity of carcinoma cells, possibly by controlling the trafficking of MT1-MMP and other components of the invasive carcinomatous program, should be further explored.

Finally, recent reports identified the nucleus as a limiting factor of invasive migration of cancer cells through a dense matrix (Harada et al. 2014, Wolf et al. 2013). Tumor cell invasion involves dynamic nuclear deformation, and 3D invasion is limited by nuclear stiffness, which is determined mostly by lamin levels (Friedl et al. 2011, Harada et al. 2014, Isermann & Lammerding 2013, Wolf et al. 2013). Below a certain pore size and above the maximal nuclear deformability, cancer cells require surface expression of MT1-MMP to enlarge matrix pores and allow for nuclear tunnel formation, whereas MT1-MMP inhibition impairs cell movement and correlates with nuclear deformation (Fisher et al. 2009; Wolf et al. 2007, 2013). Invadopodia have mechanosensing properties at the cell/matrix interface, and some level of mechanical interplay between the nucleus and invadopodia may be important for the invasive potential of tumor cells (Alexander et al. 2008, Parekh et al. 2011, Revach et al. 2015). Thus, investigators could obtain important insights into

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pathological invasion programs by determining whether and how tumor cells invading through the matrix microenvironment engage MT1-MMP exocytosis from endosomal stores in response to mechanical stress from confining collagen fibrils.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTION

P.C. wrote the review with contributions from all the other authors.

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