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REVIEW

Invadopodia: A guided tour

Inmaculada Ayala, Massimiliano Baldassarre[1], Giusi Caldieri, Roberto Buccione*

Tumor Cell Invasion Unit, Department of Cell Biology and Oncology, Consorzio Mario Negri Sud, I-66030 S. Maria Imbaro (Chieti), Italy

Abstract

The controlled degradation of extracellular matrix is crucial in physiological and pathological cell invasion alike. In cultured cells, degradation occurs at specific sites where invasive cells make contact with the extracellular matrix via specialized plasma membrane protrusions termed invadopodia. Considerable progress has been made in recent years towards understanding the basic molecular components and the ultrastructural features of invadopodia. This current knowledge will be reviewed here together with some of the most important open questions in invadopodia biology. Considering the substantial interest and momentum in the field, the need for an operational framework to correctly define and identify invadopodia will also be discussed.

Keywords: Invadopodia; Extracellular matrix; Invasion; Matrix metalloproteases; Podosomes

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Introduction

Cells in culture make contact with the extracellular matrix (ECM) through extensions of the plasma membrane that display diverse morphological features, ranging from irregular dynamic structures, e.g. lamellipodia, ruffles and pseudopodia, to more localized and highly defined protrusions, e.g. podosomes and invadopodia. All of these plasma membrane protrusions might be sensors through which cells sample the immediate extracellular environment and maintain polarized activities such as cell migration and focal degradation of the matrix (reviewed in Adams, 2002).

When invasive tumoral or transformed cells are grown on a flat ECM substratum such as gelatin, fibronectin, collagen type I, collagen type IV, or laminin

*Corresponding author. Tel.: +39 08 7257 0338; fax: +39 08 7257 0412.
E-mail address: buccione@negrisud.it (R. Buccione).
[1]Present address: Department of Pharmacology, Yale University School of Medicine, New Haven CT, USA.

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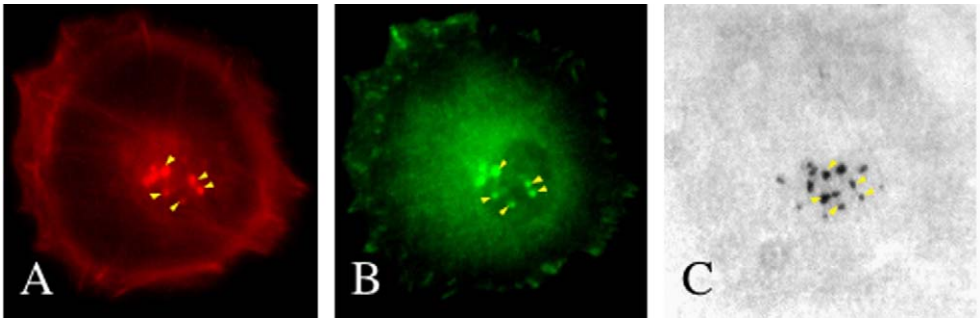

Fig. 1. Confocal laser image showing triple immunofluorescence labeling of A375MM melanoma cells plated on TRITC-conjugated gelatin: (A) invadopodial structures marked by phalloidin-Alexa 546; (B) invadopodial structures marked by Alexa 633-conjugated anti-phospho-tyrosine antibodies; (C) degradation areas on the underlying Alexa 488-conjugated gelatin. Arrowheads indicate the colocalization between actin, phospho-tyrosine and patches of degraded ECM, fulfilling the criteria for the definition of invadopodia (see "Operational definition of invadopodia").

(Kelly et al., 1994) they extend proteolytically active protrusions into the matrix from their ventral surfaces; these protrusions have been termed invadopodia (Chen, 1989; Mueller and Chen, 1991). At the fluorescence microscope, invadopodia can be recognized as actin-rich formations with underlying ECM degradation areas (Fig. 1). Although in terms of molecular characterization, invadopodia have received less attention than podosomes, a clear picture has nevertheless emerged. Invadopodial protrusions are enriched in integrins, tyrosine kinase signaling machinery, soluble and membrane proteases including matrix metalloproteases (MMPs), and quite prominently, actin and actin-associated proteins (Bowden et al., 1999; Chen, 1996; Monsky et al., 1994; Mueller et al., 1992; Nakahara et al., 1998), clearly defining them as powerhouses for the focal degradation of the ECM (Buccione et al., 2004).

Through the use of a correlative light-electron microscopy approach we found that the areas of plasma membrane contact with the substratum at sites of degradation are profound invaginations of the ventral surface of the plasma membrane measuring, on average, 8 μm wide and 2 μm deep. Many protrusions with diameters ranging from hundreds of nm to a few μm originated from these larger invaginations and sometimes penetrated into the matrix. These structures were clearly consistent with the ones originally described as invadopodia, but appeared to be part of a more complex superstructure (Fig. 2; Baldassarre et al., 2003).

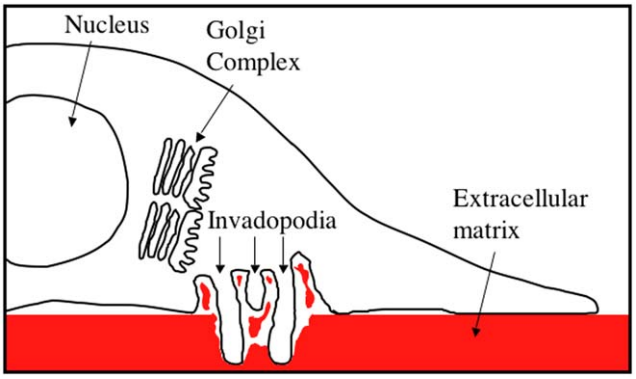

Fig. 2. Schematic diagram of the invadopodial complex based on correlative light-electron microscopy reconstructions (Baldassarre et al., 2003). Spatial relationships with the nucleus and the Golgi complex are shown. Invadopodial protrusions originate from profound invaginations of the ventral surface of the plasma membrane; within the area delimited by the large invagination, large fragments of gelatin can often be seen.

Invadopodia functions

From the beginning, invadopodia were associated with a well-defined function: focal pericellular degradation of the ECM, a crucial event in physiological ECM remodeling events such as morphogenesis, differentiation, cell migration, apoptosis, neo-angiogenesis, and in metastatic cell behavior (for a review see Basbaum and Werb, 1996). There is little doubt that the specific function performed by invadopodia is focalized degradation of the ECM in vitro; this holds true in all cell systems where they have been detected and studied. Indeed, invadopodia were first found to be precisely localized at sites of degradation of the ECM (Chen, 1989) and their enrichment in MMPs that was later defined was consistent with this biological activity. Furthermore, interfering with invadopodia components leads to direct effects on matrix degradation (Baldassarre et al., 2003; Bowden et al., 1999; Mizutani et al., 2002; Nakahara et al., 1998). Correlative light-electron microscopy also suggests that areas of ECM lysis lie close to invadopodia tips (Baldassarre, Beznoussenko and Buccione, unpublished results).