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Research paper

N-Cadherin and Fibroblast Growth Factor Receptors crosstalk in the control of developmental and cancer cell migrations

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ABSTRACT

Cell migrations are diverse. They constitutemajor morphogenetic driving forces during embryogenesis, but they contribute also to the loss of tissue homeostasis and cancer growth. Capabilities of cells to migrate as single cells or as collectives are controlled by internal and external signalling, leading to the reorganisation of their cytoskeleton as well as by the rebalancing of cell-matrix and cell-cell adhesions. Among the genes altered in numerous cancers, cadherins and growth factor receptors are of particular interest for cell migration regulation. In particular, cadherins such as N-cadherin and a class of growth factor receptors, namely FGFRs cooperate to regulate embryonic and cancer cell behaviours. In this review, we discuss on reciprocal crosstalk between N-cadherin and FGFRs during cell migration. Finally, we aim at clarifying the synergy between N-cadherin and FGFR signalling that ensure cellular reorganization during cell movements, mainly during cancer cell migration and metastasis but also during developmental processes.

1. Introduction

1.1. Cell adhesion and migration

Cell migration is a complex and central process of tissue organisation during embryogenesis and wound healing. Dysregulation of cell migration is associated with numerous diseases such as congenital malformations, neurological disorders and cancers. As a simple view, there are two main modes of cell migration, depending on cell types and cellular environment. Some cells migrate individually such as of immune system cells or fibroblasts (Friedl et al., 2001; Le Clainche and Carlier, 2008). Other cells while migrating remain associated to their neighbours inside cell cohorts or sheets, and therefore move collectively (Arboleda-Estudillo et al., 2010; Dumortier et al., 2012; Montell, 2001). Interestingly, cancer cells can migrate individually, collectively or switch from one mode to the other (Clark and Vignjevic, 2015; Friedl et al., 2012).

Cadherins, one of the core transmembrane components of *Adherens Junctions* (AJs) play an essential role during these processes. For instance, E-cadherin is critical for border cell migration in *Drosophila* egg chamber (Niewiadomska et al., 1999) or for directional epithelial sheet migration during wound healing in mouse cornea (Danjo and Gipson, 1998). Another cadherin, N-cadherin is a major regulator of neuronal progenitors migration (Kadowaki et al., 2007; Lien et al., 2006). Moreover, the switch from E-cadherin to N-cadherin expression during Epithelial to Mesenchymal Transition (EMT) confers to epithelia-originating cancer cells drastic changes in their migratory behaviour (Li et al., 2001; Nakashima et al., 2003; Rieger-Christ et al., 2004; Taeger et al., 2011; Kolijn et al., 2015).

FGFRs (Fibroblast Growth Factor Receptors) belong to a family of single pass transmembrane Receptors Tyrosine Kinases (RTK). Activation of FGFRs, elicited by the binding of their ligands FGFs, trigger numerous intracellular signalling pathways orchestrating key cellular events including cell migration (Lemmon and Schlessinger, 2011). For example, FGFR 1 and 2 have been reported as key regulators for keratinocyte migration in wounded mouse skin (Meyer et al., 2012). During *Drosophila* tracheal morphogenesis, interaction of FGFR signalling with the regulation of the actin network is regulating cell migration (Okenve-Ramos and Llimargas, 2014). Remarkably, a functional link between FGFR signalling and cadherin-mediated adhesion has been reported for the regulation

Abbreviations: AJ, *adherens* junction; CAFs, cancer-associated fibroblasts; CNS, central nervous system; DN, dominant negative; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial to mesenchymal transition; FA, focal adhesion; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FRS2a, FGFR substrate 2a; GC, granulosa cell; GF, growth factor; KD, kinase death; mEpiSC, mouse epiblast stem cell; ROSE, ovarian surface epithelial cell; RTK, receptors tyrosine kinase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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of neural or tumour cell migration (Suyama et al., 2002; Williams et al., 2001). The synergistic action of these two transmembrane proteins would thus provide an unexpected additional level of regulation of cell migration.

1.2. Individual and collective cell migration modes

Numerous culture systems have been developed to study the migration of individual cells *in vitro* and the most used is the well-known Boyden chamber (Boyden, 1962). Recent progresses in micro-fabrication techniques brought out the possibility to produce one-cell-size adhesive areas with different protein surfaces (Maiuri et al., 2012), providing powerful tools to control and study the mode of migration of single cells.

Most of the cells migrate individually through a cyclic process involving adhesion/de-adhesion and acto-myosin polymerisation/contractility phases (Blanchoin et al., 2014; Krause and Gautreau, 2014). The successive steps are: the induction of cell polarity, the protrusion of the leading edge by actin polymerisation, the attachment of protrusive membrane to new adhesion sites or Focal Adhesions (FAs) on the Extra Cellular Matrix (ECM), and the contraction of acto-myosin to promote the sliding and detachment of the cell rear. Attachment/detachment of the cell from the ECM is one of the most important checkpoints in this process of so-called lamellipodial migration.

However, this mode of migration is not universal as revealed, by *in vivo* and *in vitro* studies of cell migration performed by immune surveillance cells (or dendritic cells) exiting the blood flow to patrol in tissue upon inflammation or cancer cell migration (Friedl et al., 2001). The development of micro-channel assays to study cell migration in confined environment of well-defined geometry (Heuzé et al., 2011; Vargas et al., 2014) allowed to demonstrate that dendritic cells perform single cell migration by a totally different mode, the so-called amoeboid migration (Friedl and Wolf, 2010; Paluch et al., 2006). Amoeboid migration refers to cells of round morphology that do not form adhesions with the substratum and thus lack FAs and stress fibres. Amoeboid cells insteat migrate by forming membrane blebs at their front, materialized by a disruption of the plasma-membrane actomyosin cortex link, then by the reconstitution of the actomyosin network within the protruding bled (Smith et al., 2007; Yoshida and Soldati, 2006). In a confined environment amoeboid cells migrate by pushing laterally on their environment thanks to a retrograde intracellular actomyosin flow (Paluch et al., 2006).

Epithelial, glial and some cancer cells migrate collectively. The simplest approach to study collective migration *in vitro* is the 2D migration of cell sheets on a cell-free surface in wound scratch assays (Cory, 2011) or after the release of a constraint barrier on an ECM-coated surface (Van Horssen and ten Hagen, 2011; Vedula et al., 2014). In this case, cells at the front, as well as some cells inside the group, migrate through lamellipodial mode; however, they remain attached to their neighbours allowing them to improve their migration efficiency and to acquire emerging collective properties (Ladoux et al., 2016). As a result, AJs and their ligands, cadherins, play a primordial role in this mode of cell migration (Trepat et al., 2009; Vedula et al., 2012). The maintenance of intercellular adhesion allows cells to migrate on the substrate by a tug of war mechanism (Ladoux et al., 2016). Embryonic cells, especially during gastrulation (Aman and Piotrowski, 2010), as well as differentiated epithelial cells during wound healing (Arciero et al., 2011; Trepat et al., 2009; Vedula et al., 2012) follow this mode of migration.

1.3. Migration of cancer cells

Tumor cells engage the two modes of migration in order to reach and invade distant tissues (Friedl and Wolf, 2003). Local invasion is the result of protruding cohorts of cells that still maintain the contact with the primary tumour. This invasive mode is observed in epithelial cancers such as oral squamous cell carcinoma, mammary carcinoma and colon carcinoma (Friedl et al., 2012). On the contrary, isolated or/and clusters of cancer cells can completely detach from the primary tumour to invade distant tissues as seen in melanoma in lung cancer, breast cancer and melanoma (Friedl et al., 2012). Finally, cells can detach from each other to escape and migrate individually. In this case, either cells migrate as mesenchymal cells with the formation of a lamellipodium adhering and pulling on the ECM at the leading edge and an uropod, or cells adopt and amoeboid morphology-like and squeeze to glide through the matrix (Friedl and Wolf, 2010; Friedl et al., 2012). This type of migration occurs in lymphoma and small cell lung cancer, leukemia or mesenchymal type like fibrosarcoma and glioblastoma tumours. Apart from intrinsic properties, the ability of cancer cells to migrate enormously depends on adhesion to the surrounding tumour microenvironment, and especially to cancer-associated fibroblasts (CAFs) which can increase their migratory and invasive characters, as reported for colorectal cancer cells (Lorusso and Rüegg, 2008).

To summarize, cancer cells can migrate individually or collectively, depending of their origin. In the latter case, reinforcing adhesion with their neighbours may foster their collective migration by increasing the efficiency of the tug of war mechanism (Trepat et al., 2009). Therefore, under these different conditions, cell-cell adhesion could contribute to promote or inhibit migration, and cadherins appear thus as potential key regulators of cancer cell migration and metastasis.

2. Cadherins, tissue organization and cell migrations

Cadherins constitute the most important family of cell-cell adhesion molecules (Takeichi, 1990). We will consider here a subtype of these molecules, the so-called classical cadherin subfamily: E (Epithelial)-, N (Neuronal)-, P (Placental)- and R (Retinal)-cadherins and the closely related VE (Vascular/Endothelial)-cadherin. These integral plasma membrane proteins are the intercellular ligands of AJ. They are equally involved in biochemical and mechanical signals transduction at AJ (Ladoux et al., 2015; Mège et al., 2006). Cadherin functions require the association of their cytoplasmic domain to catenins (α, β and p120), which connect them to actin filaments maintained under tension by myosin II motors. Besides this role in the mechanical linkage of AJ to actin, catenins associate to various structural and signalling proteins involved in the regulation of cadherin functions and/or in signalling cascades downstream of cell-cell contact formation (Hoffman and Yap, 2015; Padmanabhan et al., 2015).

2.1. Role of N-cadherin in cell migration during nervous system development

N-cadherin is mainly expressed in neural and mesenchymal tissues. It controls various migration processes responsible for tissue organization in different systems and organs: brain, spinal cord and nerves, lens, muscle and blood vessels. N-cadherin is ubiquitously expressed in the nervous system at the initiation of neurulation (Duband et al., 1987; Radice et al., 1997). It is required for proper cohesion and polarisation of neuroepithelial cells, and for migration of neuronal progenitors from their first location in the neuroepithelium to their final destination as mature neurons or glial cells.