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REVIEW

Interstitial cell migration: integrin-dependent and alternative adhesion mechanisms

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Abstract Adhesion and migration are integrated cell functions that build, maintain and remodel the multicellular organism. In migrating cells, integrins are the main transmembrane receptors that provide dynamic interactions between extracellular ligands and actin cytoskeleton and signalling machineries. In parallel to integrins, other adhesion systems mediate adhesion and cytoskeletal coupling to the extracellular matrix (ECM). These include multifunctional cell surface receptors (syndecans and CD44) and discoidin domain receptors, which together coordinate ligand binding with direct or indirect cytoskeletal coupling and intracellular signalling. We review the way that the different adhesion systems for ECM components impact cell migration in two- and three-dimensional migration models. We further discuss the hierarchy of these concurrent adhesion systems, their specific tasks in cell migration and their contribution to migration in three-dimensional multi-ligand tissue environments.

Keywords Cell adhesion · Cell migration · Integrins · Extracellular matrix · Cytoskeleton

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Introduction

Cell adhesion and migration are fundamental to the formation and maintenance of multicellular organisms. Cell adhesion is provided by adhesion molecules, which are expressed at the cell surface of all nucleated cells, mediate extracellular binding to cell and tissue substrates and transmit mechanical docking to the intracellular actomyosin or intermediate filament cytoskeleton. Cell adhesion underlies many important physiological processes, including cell spreading, polarity, anchoring and differentiation. When cell-tissue interactions undergo dynamic turn-over, adhesion molecules further mediate cell migration and positioning during dynamic phases of the body, including morphogenesis, wound healing and, in a de-regulated form, during cancer invasion and metastasis (Hood and Cheresh 2002; Hynes 2002). Likewise, cell adhesion and migration underlie many functions of the immune system, including leukocyte recirculation, pathogen recognition and effector function (Friedl and Weigelin 2008).

To fulfil these various tasks in the different cell types and tissue contexts, diverse sets of adhesion receptors contribute to cell interaction with tissue components and to migration. Adhesion receptor ligands are another cell, a multimeric particle or macromolecules that are immobilized in the tissue, such as extracellular matrix (ECM) ligands. Important ECM proteins recognized by adhesion receptors are collagens, fibronectin, vitronectin, fibrinogen and laminin (van der Flier and Sonnenberg 2001). Non-protein ECM ligands comprise proteoglycan polysaccharides, such as heparan sulphate, chondroitin sulphate and keratin sulphate, and the non-proteoglycan polysaccharide hyaluronan (Iozzo 1998; Heino and Kapyla 2009).

Several classes of cell surface receptors fulfil adhesion and cytoskeletal coupling functions and provide a range of

adhesion strength, specificity and turn-over rates during cell migration (Fig. 1). High affinity adhesion to ECM ligands is predominantly provided by receptors of the integrin family (Hynes 2002) and CD44 (Goodison et al. 1999). Whereas integrins predominantly recognize extracellular protein scaffolds, such as interstitial collagen (Takada et al. 2007), CD44 preferentially binds to extracellular carbohydrate polymers, such as glycoproteins, glycosaminoglycans and hyaluronic acid (HA; Ponta et al. 2003). In addition to these "classical" adhesion receptors, other surface receptors can bind ECM components and induce signalling, including the syndecans (Bernfield et al. 1999) and the receptor tyrosine kinases discoidin domain receptors (DDRs; Yoshimura et al. 2005). Whereas integrin- and CD44-mediated adhesions have previously received substantial attention (Humphries et al. 2003), alternative adhesion mechanisms and their contribution to cell anchoring and migration have been less well studied. We summarize here the way that integrin- and non-integrin-mediated cell-substrate interactions contribute to different types of cell migration.

Modes of cell migration and adhesion requirements

Cell migration is not a uniform event but comprises distinct modes of cell migration that are executed by different cell types and contexts. These migration types vary in cell shape, adhesion strength and migration speed and also in whether cell-cell junctions are retained (Fig. 2).

Arguably, the most "simple" migration mode is amoeboid migration (Friedl et al. 2001). Cells that move in an amoeboid manner include primordial germ cells, lymphocytes, dendritic cells, lymphoma cells and neutrophils, all of which exhibit low or no integrin-mediated traction force generation (Entschladen et al. 1997; Friedl et al. 1998; Blaser et al. 2006; Lammermann et al. 2008). These cells form relatively instable adhesion sites to a substrate; such sites rapidly turnover and, depending on extracellular context and signalling, allow for rapidly adaptive migration (Friedl et al. 2001). Amoeboid movement is driven by a roundish to ellipsoid cell shape, non-focalized but rather diffusely organized adhesion sites to the substrate and a strictly cortical actin cytoskeleton that lacks stress fibres (Friedl and Wolf 2003). Two types of

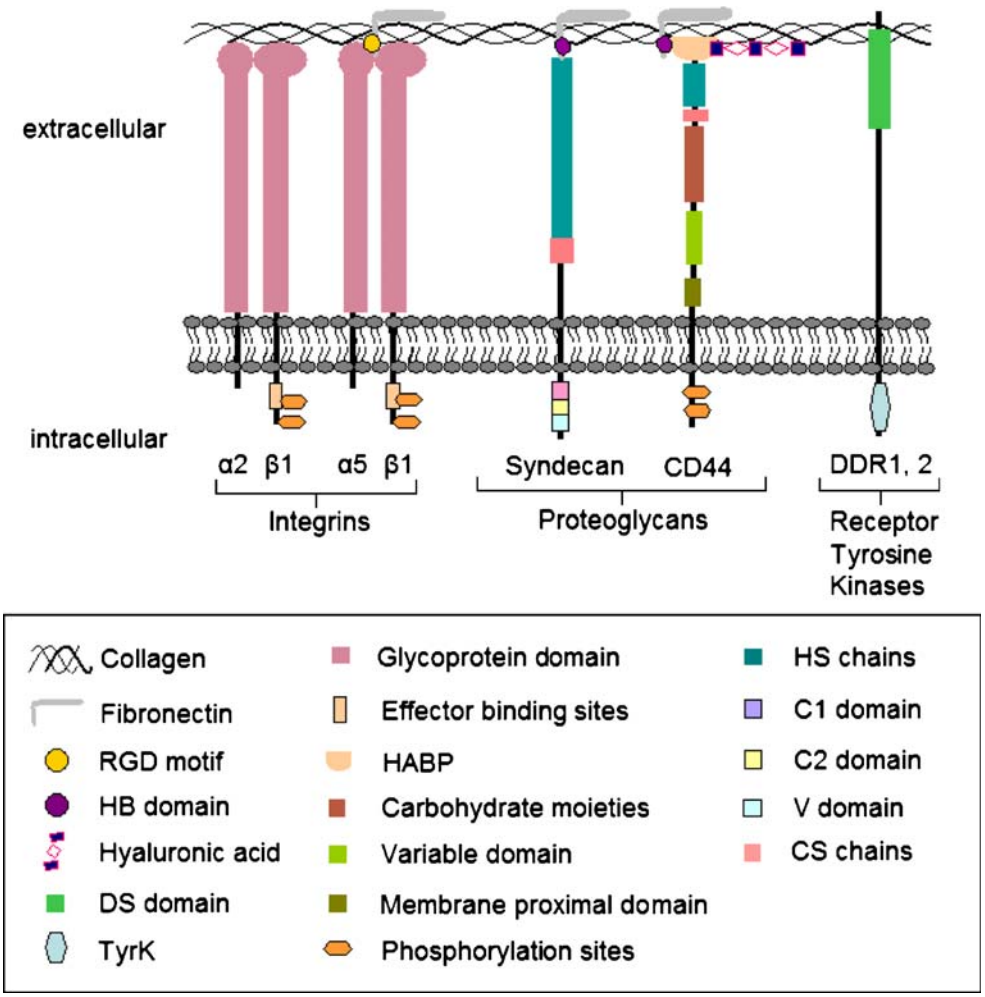

Fig. 1 Classes of adhesion receptors involved in cell adhesion and migration. Important domains of adhesion receptors and interstitial ECM ligands collagen, fibronectin and hyaluronan are shown

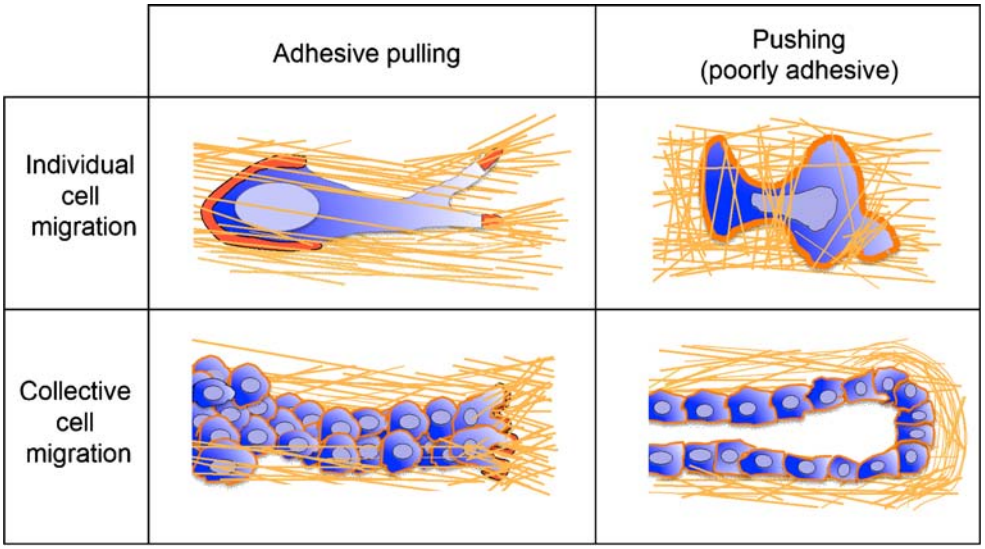

Fig. 2 Various migration strategies. Dependent on cell-matrix adhesion strengths and cell contrctility, force generation occurs either via attachment to the ECM substrate and pulling or by cell propulsion. Dependent on the stability of cell-cell adhesion, cells migrate either individually or within multicellular strands (*red* actin cytoskeleton)

force generation contribute to amoeboid movement. Based on relatively weak attachment and speading to the substrate, a fast "gliding" type of movement is enabled that supports a weakly adhesive pulling-type migration across two-dimensional (2D) and in three-dimensional (3D) environments (Friedl and Wolf 2009). Alternatively, in non-adhesive cells, polarized dendrite or bleb formation coupled to rear-retraction fail to attach to 2D substrate and lack adhesion sites and, thus, provide an intercalating propulsive-type of migration in 3D tissues (Fackler and Grosse 2008). The biophysical basis of this blebbing-type migration is incompletely understood as it shows signs of adhesion-independent migration. Instead of focalized adhesion complexes, a predominantly cortical actin cytoskeleton drives cell polarization and physical translocation by shape change and cytoskeletal stiffness in complex tissue environments (Paluch et al. 2006; Friedl and Wolf 2009). In cells with increased adhesion and cytoskeletal contractility, cell-matrix interactions become focalized and the cell adopts an elongated spindle-shaped morphology; this mode of migration is termed mesenchymal migration and is used by fibroblasts, myoblasts and many cancer cells (Friedl et al. 1998; Friedl 2004), generates substantial adhesion and traction force towards the surrounding tissue and further mediates proteolytic tissue remodelling by the function of cell-produced proteases (Wolf and Friedl 2009). Both ligand binding and intracellular coupling of cell adhesions are turned over in the range of minutes to hours thereby regulating both local adhesion strength and the dynamics of the cell (Zamir and Geiger 2001; Ballestrem et al. 2001). During morphogenesis, regeneration and cancer invasion, cells that retain cell-cell junctions by means of cadherins and other cell-cell adhesion mechanisms migrate collectively either as monolayer sheets or as 3D strands, sprouts or isolated clusters (Friedl et al. 2004). Two types of force generation in collective migration are under discussion at present, depending on the amount of anterior adhesion and traction force generation. If one or several front- and mid-row cells generate adhesion and traction force towards the substrate, collective migration results from adhesive "pulling" mediated by adhesion-complexes that connect to the actin cytoskeleton, similar to mesenchymal movement (Hegerfeldt et al. 2002; Trepat and Wasserman 2009). This type of migration is commonly detected in sprouting vessels, epithelial sheets during wound healing and cancer invasion (Hegerfeldt et al. 2002; Friedl and Gilmour 2009). A second, less well understood mode of collective force generation is multicellular pushing, which is produced by a stable stick-like stalk and a relatively roundish terminal bud that protrudes into soft tissue in the absence of apparent force-generating adhesion complexes (Ewald et al. 2008). Thus, different cellular and molecular requirements for adhesion and force generation govern the different types of cell migration. Whereas, until recently, integrins have received ample attention and are considered as the main mediators of adhesion force generation during cell migration, the promigratory functions of non-integrin adhesion systems remain to be integrated into these concepts of cell movement.

Integrins

Integrins are heterophilic cell adhesion molecules consisting of non-covalently connected α and β chains that together determine ligand-binding specificity and intracellular coupling (Humphries 2000; Hynes 2002). Based on ECM/ligand recognition, integrins mediate binding to laminins (α2β1, α3β1, α6β1, α7β1), fibrillar collagens (α1β1, α2β1, α3β1, α10β1, α11β1) and Arg-Gly-Asp (RGD) motifs contained in many ECM proteins (α5β1,

αvβ3, αvβ5, αIIbβ3; Takada et al. 2007). Thereby, integrins are the most important cell surface receptors for cell interactions with ECM structures.

Integrins control the strength and turn-over of cell interactions with ECM scaffolds (Hynes 1992). After ligand binding, integrins multimerize in the plasma membrane in a focalized manner and connect, via intracellular signalling and adaptor proteins, to the actin cytoskeleton, termed focal contact or focal adhesion (Burridge and Chrzanowska-Wodnicka 1996; Zaidel-Bar et al. 2007; Moser et al. 2009). Alternatively, diffuse integrin distribution devoid of microscopically detectable clustering and focalization of adhesion site mediates substrate binding and intracellular signalling (Friedl et al. 1998).

To mediate cell movement, the integrin-mediated cell-substrate interactions and linkages to the actin cytoskeleton form and turn-over, the dynamics and polarity of which determine cell speed and directional persistence. The way that integrins govern migration type and rates depends upon net adhesion strength per cell, type of cell-matrix interactions and type of substrate. On 2D ECM substrates, including collagen, fibronection or vitronectin, integrin-mediated adhesions are preferentially mediated by α5β1, αvβ3 and α2β1, respectively (Takada et al. 2007). In integrin-dependent migration models, the highest velocities result from an intermediate level of net adhesion strength allowing both rapid focal contact formation and the generation of traction forces, which are regulated by the small GTPase Rho (DiMilla et al. 1991; Beningo et al. 2006) . Accordingly, increasing adhesion to the substrate slows cells down and favours cell immobilization and anchoring attributable to delayed rear-retraction. Likewise, at low net adhesion, migration rates are impaired because of reduced binding strength and force generation at the leading edge, resulting in partial or complete loss of migration (Palecek et al. 1997). The impact of adhesion- and traction force-dependent integrin functions are commonly established in haptokinetic migration across a 2D ligand-coated substrate, so that some degree of attachment is indispensible for migration (Huttenlocher et al. 1995). This principle of adhesion-driven migration applies to many, if not all, actin-associated integrins, notably β1, β2, β3, and β4 integrins (Rabinovitz and Mercurio 1997; Maaser et al. 1999; Vicente-Manzanares et al. 2009). Consequently, both cell adhesion and migration are impaired by adhesion-perturbing anti-integrin antibodies or genetic deletion of integrins so that the cells either round up and partly detach or completely lose contact to the substrate (Friedl and Wolf 2003). If, however, cells move through a 3D ECM, distinct physical principles apply because cells are entirely surrounded by ECM and, even after loss of adhesion, continue to interact passively with the substrate (Friedl and Brocker 2000).

For cells of high integrin availability moving through a 3D ECM, including fibroblasts and certain cancer cells, integrins mediate adhesive pulling at the leading edge so that traction force towards the substrate is continually being generated (Fig. 2; Maaser et al. 1999; Petrie et al. 2009). Consequently, cell elongation and mesenchymal migration are dependent on integrin-mediated adhesion and focalization of the actin cytoskeleton to matrix contacts. The integrin engagement leads to the activation of focal adhesion kinase, Rho/Rac guanine nucleotide exchange factors and Rho kinase (ROCK), which together drive the formation and turn-over of adhesions (Iwanicki et al. 2008). Following interference with integrin-mediated adhesion, mesenchymal migration is abrogated and no alternative adhesion receptors compensate for ablated integrin-dependent force generation and mesenchymal migration (Maaser et al. 1999; Grinnell 2008, 2009). In mesenchymal migration, integrin β1 or αvβ3 integrins cooperate with cell surface proteases, notably matrix metalloproteinases (MMPs) leading to the generation of small microtracks bordered by remodelled collagen fibres (Deryugina et al. 1998; Wolf et al. 2007). Secondary to traction force generation, mesenchymal migration leads to contraction and remodelling of the ECM in vitro and to wound healing (Cooke et al. 2000; Larsen et al. 2006).

If integrin-mediated traction force is low or negligible, moving cells utilize the amoeboid migration mode (Fig. 2; Friedl et al. 2001). Whereas, on 2D surfaces, amoeboid migration is still dependent on low adhesion mediated by integrins (Lammermann et al. 2008), amoeboid migration in 3D fibrillar collagen or interstitial tissue in vivo persists either partly or fully after integrins are blocked by antibody or are genetically ablated (Friedl et al. 1998; Lammermann et al. 2008). In integrin-independent amoeboid migration, the leading edge produces pseudopodia, dendites or roundish-shaped blebs, all of which are dependent on cortical actin networks but do not form focalized adhesion complexes with the ECM substrate (Friedl et al. 1998; Lammermann and Sixt 2009). The mechanisms underlying integrin-independent migration are incompletely unterstood but are best explained by actin forward flow followed by cell intercalation between matrix pores and gaps and cell contraction mediated by myosin II to move both the cell rear and the nucleus forward (Lammermann et al. 2008). Thus, grossly different magnitudes of integrin-mediated adhesion and force generation are associated with the diverse migration modes.

Accordingly, in 3D ECM-based models, cells can switch between high and low integrin-dependence of migration. The lowering of integrin-mediated adhesion by blocking with antibodies or by interfering with the integrin-effector c-src does not abrogate migration of cancer cells in 3D ECM-based models but is followed by persistent robust cell

movement (Carragher et al. 2006; Zaman et al. 2006). Whether such plasticity is restricted to cancer cells and which alternative adhesion mechanisms compensate for impaired integrin function remain unclear.

Because of their multifunctional nature and ubiquitous expression, integrins contribute to most cell-tissue interaction models substantially and impact other adhesion pathways in response to ECM. Thus, as we will discuss below, the study of adhesion mechanisms other than integrins is often compromised by an overlap with integrin-mediated substrate recognition and function.

Syndecans

Syndecans are a familiy of transmembrane cell surface heparan sulphate proteoglycans (HSPGs) with four members, syndecan 1–4. All vertebrate cells express at least one syndecan family member in a cell-type and tissue-specific manner, which is further modified during cell activation (Tkachenko et al. 2005). Syndecans bind to ECM ligands and further cooperate with other cell surface receptors for ligand-binding and signalling. Via their heparin-binding ectodomain, syndecans bind to extracellular glycosaminoglycans, including heparan sulphate and chondroitin sulphate, and to other ECM molecules, including collagen types I, III and IV, fibronectin and vitronectin (Beauvais et al. 2004). By distinct mechanisms, syndecans further bind via residues within the HSPG side chains to cytokines and growth factors, including fibroblast growth factor-2 and epidermal growth factor and "present" them laterally to their specific receptors (Wu et al. 2003; Tkachenko et al. 2005).

Syndecans mediate both cell adhesion and co-signalling, often in the same context, which renders the distinction between adhesion and co-signalling function difficult, if not impossible. In most cell models, overexpression of syndecans enhances cell adhesion and haptokinetic migration in normal and neoplastic cells, whereas interference with syndecan function decreases cell migration (Table 1). As an example, in endothelial cells, binding of syndecan-4 to fibronectin-cated substrate results in syndecan-4 co-clustering with integrin $\alpha 5\beta 1$ and the activation of Rac-1 through the intracellular scaffold protein synectin (Tkachenko et al. 2006; Morgan et al. 2007). Consequently, syndecans enhance cell spreading, polarization and migration in vitro and cell migration and tissue remodelling during wound healing and angiogenesis in vivo (Table 1; Echtermeyer et al. 2001; Stepp et al. 2002; Morgan et al. 2007).

Syndecans interact with a large number of ligands, which in parallel also bind to other cell surface receptors. Thus, a functional synergy between syndecans and integrins leads to an overlap in adhesion-dependent signalling pathways (Morgan et al. 2007). Given that syndecans functionally synergize with integrins, the extent to which syndecans can be understood as true adhesion receptors awaits further clarification by using models that isolate the direct contribution of syndecans to adhesion from its co-receptor and signalling activities.

Discoidin domain receptors (DDR)

Discoidin domain receptors (DDRs) belong to the discoidin-like domain-containing subfamily of receptor tyrosine kinases, with two members in mammalian cells: DDR1, expressed as five isoforms (DDR1a-e), and DDR2 with no known isoforms (Alves et al. 2001; Vogel et al. 1997). As main ligands, DDRs bind to all triple-helical fibrillar collagens, and DDR1 additionally binds to collagens type IV, VI and VIII (Curat et al. 2001). DDR1 is expressed in many epithelia (Vogel et al. 1997), and in tissue-infiltrating leukocytes (Kamohara et al. 2001), whereas DDR2 is expressed in muscle cells, kidney, lung, brain and connective tissue (Vogel 1999); both DDRs are upregulated in many cancer cell types (Vogel et al. 2006). After ligand binding, DDRs induce various intracellular signalling pathways, including the activation of Wiskott-Aldrich syndrome protein and Pyk-2s, the SH2-domain-containing-transforming protein and SH2-domain-containing phosphatase 2, all of which indirectly promote actin dynamics (Buday et al. 2002; Koo et al. 2006; Vogel et al. 2006). Accordingly, DDRs enhance cell migration, proliferation, and survival (Vogel 1999). In contrast to other receptor tyrosine kinases, initial signalling through DDRs occurs within minutes but peaks only several hours later, implicating DDRs in sustained and slow rather than acute responses to the ECM (Vogel et al. 1997, 2006).

Despite their collagen-binding capability, whether DDRs can be considered as classical adhesion receptors is unclear. DDR signalling typically co-engages with integrins (Shintani et al. 2008). DDRs enhance integrin-mediated cell adhesion to collagen (Kamohara et al. 2001) and enhance integrin-mediated signalling (Shintani et al. 2008). In addition, in some models, DDR1 overexpression enhances cell attachment to collagen that cannot be directly attributed to integrin function, suggesting either a direct adhesion function of DDR1 or the coengegement of yet another adhesion system (Kamohara et al. 2001).

DDRs regulate cell migration in an isoform-specific manner. DDR1a-overexpressing leukemia and glioma cells show enhanced migration into 3D collagen lattices, whereas overexpression of DDR1b reduces migration in both cell types (Kamohara et al. 2001; Ram et al. 2006). On the basis

Table 1 Regulation of cell migration by syndecans (*2D* two-dimensional, *3D* three dimensional)

Syndecan type	Cell type	Experimental model	Function	Reference
Syndecan-1	Breast cancer cells	2D spreading and migration assay; migration through 3D matrigel after overexpression	Increased spreading, adhesion and migration on 2D collagen I; increased cell invasion in 3D Matrigel	Burbach et al. 2004
	Myeloma cells	In vivo model of experimental metastasis in mice	Increased metastasis and tumour growth	Khotskaya et al. 2009
Syndecan-2	Intestinal epithelial cells	2D adhesion and migration after overexpression	Increase of adhesion, spreading on collagen type I (in cooperation with $\alpha 2\beta 1$ integrin)	Choi et al. 2009
	Colon carcinoma cells	Migration across type-I-collagen-coated surface after overexpression	Increased migration speed	Park et al. 2002
	Melanoma cells	Migration through polycarbonate filter (transwell) after overexpression	Increased migration and invasion	Lee et al. 2009
Syndecan-3	Neuronal cells	Migration through polycarbonate filter (transwell)	Increased migration	Hienola et al. 2006
Syndecan-4	Melanoma cells	Adhesion and migration across fibronectin-coated 2D surface	Increased adhesion and migration	Chalkiadaki et al. 2009
	Fibroblasts	Adhesion and migration in 3D fibrin-fibronectin-matrix	Increased adhesion and migration	Midwood et al. 2004, 2006

that all DDRs bind to collagen by a similar mechanism, the signalling pathways that underlie such different fine-tuning of migration are unknown.

DDRs not only enhance cytoskeletal dynamics but further induce a more complex "invasion program". DDR signalling upregulates pro-invasive MMPs 2 and 9, which leads to enhanced proteolytic degradation of ECM (Hou et al. 2002) and invasion and metastasis of tumour cells in vivo (Vogel et al. 1997). Although experimental overexpression of DDR1 acts in a promigratory manner (Ram et al. 2006), whether lower endogenous levels mediate the same effect remains unclear. To improve the discrimination between adhesive and signalling functions of DDRs, future studies should address DDR adhesion and other functions in integrin-independent models.

CD44

CD44 is a highly glycosylated member of the hyaladherin or link protein superfamily of adhesion molecules and is either expressed as the standard form (CD44s) or as one of 12 distinct isoforms (CD44v1-v12; Ponta et al. 2003; Naor et al. 2008). CD44 binds its main ligand, HA, via the hyaluronan-binding domain (Banerji et al. 2007). Other ligands, which instead interact with variable membrane-proximal domains of CD44, include heparan sulphate (exon v3), chondroitin sulphate (exon 5) and, via unmapped sites with probably weaker binding strength, collagen types I and VI, fibronectin and laminin and cell surface receptors, such as E- and L-selectin (Ponta et al. 2003; Bendall et al. 2004; Naor et al. 2007). The cytoplasmic domain of CD44 recruits the actin-binding proteins ezrin, radixin and moesin (ERM; Legg et al. 2002) and ankyrin and thereby physically bridges extracellular ligands to the actin cytoskeleton and induces intracellular signalling (Bourguignon 2008; Singleton et al. 2004). In addition to its adhesion function, CD44 serves as a co-receptor for other signalling receptors, such as the receptor tyrosine kinase mesenchymal-epithelial transition factor (c-Met), epidermal growth factor receptor and tumour growth factor-β (Orian-Rousseau et al. 2002).

CD44s is expressed by all nucleated vertebrate cells, including most cancer cells (Naor et al. 1997; Tanabe et al. 1993). Activated cells and many cancer cells additionally express CD44 variants, such as CD44v3-v10 on keratinocytes and CD44v6 on many transformed cells ((Brown et al. 1991); Wang et al. 2009). CD44-mediated signalling occurs via various pathways. HA binding leads to the activation of several effectors, including c-Src (Ouhtit et al. 2007), Rac1 and RhoA (Bourguignon et al. 2000; Bourguignon et al. 2001). In turn, active Rho and its effector ROCK promote the recruitment of the cytoskeleton-protein ankyrin-1 and engage with the conserved cytoplasmic domain of CD44 and thereby provide a second link between CD44 and the actin cytoskeleton (Singleton and Bourguignon 2004).

In addition to binding to tissue-anchored HA, CD44 immobilizes HA at the cell surface (Rilla et al. 2008). In early cell adhesion, cell-surface-tethered HA captures ECM substrata prior to integrin-mediated focal contact formation (Zimmerman et al. 2002). Cell-surface HA is constitutively

present at the tips of cell protrusions, such as pseudopodia and lamellipodia, and engages with extracellular ECM substrate before integrin clustering and the formation of focal adhesions are detectable (Zimmerman et al. 2002; Rilla et al. 2008).

In most 2D haptokinetic migration models, CD44 enhances migration, either directly by mediating attachment to the substrate or by enhancing promigratory signalling. In normal and neoplastic cells, CD44 supports adhesion and migration across HA-coated surfaces (Zhu et al. 2006). Hereby, in contrast to integrins and syndecans, CD44 does not cluster at contact sites but rather seems to form uniform interaction zones to the substrate with a trend for redistribution to the cell rear (Jacobson et al. 1984; Goebeler et al. 1996; Friedl et al. 1997). In migrating leukocytes, CD44 is virtually excluded from the leading edge and accumulates together with ERM proteins in the posterior uropod, albeit that its function here is unclear (Sanchez-Madrid and del Pozo 1999; Wagner et al. 2008). Many cells, irrespective of adhesion strength and the substrate across which they migrate, release substantial amounts of CD44, the function of which however is unclear, from the rear of the cell (Bazil and Horejsi 1992; Friedl et al. 1997). In addition to an adhesion function, the CD44-HA interaction results in the rapid activation of surface proteolysis via endopeptidases, including MT1-MMP and ADAMs (a disintegrin and metalloproteinase family), which cleave the CD44 ectodomain and thereby limit CD44-mediated cell attachment (Nagano et al. 2004). Thus, the dual role of CD44 comprises cell attachment and the secondary release of CD44-mediated adhesion bonds.

In contrast to in vitro findings with respect to the contribution of CD44 to cell migration on an HA substrate, CD44-deficient mice lack obvious defects of development, regeneration and immune function, suggesting intact interstitial cell migration (Protin et al. 1999; Naor et al. 2008). To what extent other adhesion receptors, including β1 integrins, the receptor for hyaluronan-mediated motility (RHAMM) or layilin as alternative receptors for HA compensate for the loss of CD44 remains to be addressed (Protin et al. 1999; Naor et al. 2007; Chen et al. 2008).

In cancer models, the interaction of CD44 variants with HA supports lymphoma and melanoma progression and metastasis, which is prevented by blocking antibodies targeting CD44v4-v10 or by expressing CD44 with an inactive HA-binding domain (Wallach-Dayan et al. 2001). Conversely, over-expression of soluble CD44 ectodomain in malignant melanoma and mammary carcinoma cells inhibits growth, local invasion and metastasis in vivo, suggesting a role for the membrane-anchoring of CD44 (Ahrens et al. 2001; Peterson et al. 2000). However, given the lack of a phenotype in CD44-deficient mice, the in vivo relevance of CD44-mediated adhesion and migration detected in vitro remains unclear. Thus, like syndecans, CD44 and its variants provide multiple adhesion and co-signalling functions, the mechanistic contribution of which to cell migation remains incompletely understood.

Concluding remarks

The various adhesion systems expressed by vertebrate cells serve overlapping functions for cell positioning, anchoring and signalling but simultaneously retain additional independent and unique properties for each receptor. Whereas the molecular structure and associated signalling machinery of each receptor system have been examined in detail, only the role of integrins in cell migration has been conclusively established. Conversely, the functions of syndecans, DDRs and CD44 in the different types of cell migration, their integration into distinct adhesion and de-adhesion functions of the cell, their functional overlap and their spatiotemporal coordination during cell-matrix interaction and migration within multi-ligand enviroments remain unknown. Syndecans and DDRs cooperate with integrins synergistically in mediating cell adhesion and migration; this compromises defined experimental control of their functions. In order to experimentally overcome the governance of integrins and to gain better conceptual insights into each adhesion system independently, future strategies will require models of limited integrin availablility or integrin deficiency. Integrin-deficient cell models that still retain their cytoskeletal and polarization machinery will be instrumental in addressing specific migration modes and mechanisms and their response to physical tissue properties. To this end, the discrimination of the bona fide adhesion function of DDRs, syndecans and CD44 from their other co-receptor functions and from intracellular docking to cytoskeletal and signalling scaffolds, which contribute to cell adhesion and migration by indirect routes, will be of importance. Such approaches will clarify the way that distinct adhesion systems spatiotemorally contribute to the complex process of cell dynamics and of anchoring in multifaceted tissue environments.

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