Introduction

The ability of cells to adopt a variety of shapes, and to carry out coordinated and directed movements, as well as the establishment of cell-cell and cell-substrate contacts, depends on the dynamic assembly and reorganization of the F-actin cytoskeleton. Rho-family GTPases (e.g. Cdc42, Rac1, RhoA) are important regulators of actin-cytoskeleton-dependent processes such as morphogenesis, adhesion and migration (Ridley, 2001; Etienne-Manneville and Hall, 2002; Malliri and Collard, 2003). Rho-family proteins can be involved in malignant transformation and tumor invasion, as shown for T-lymphoma, carcinoma, hepatoma and melanoma cells (Price and Collard, 2001; Jaffe and Hall, 2002; Sahai and Marshall, 2002). In contrast to oncogenic Ras proteins, which are constitutively activated by point mutations, the function of Rho-like GTPases in oncogenic transformation is attributed to an increased expression level and/or deregulated activity of their regulators.

The Rac-specific guanine nucleotide exchange factor (GEF) Tiam1 is one important regulator of Rho GTPase functions in tumor cells (Mertens et al., 2003). Through Rac activation, Tiam1 induces T-lymphoma invasion and metastasis but also inhibits migration and invasion of human renal cell carcinoma (Habets et al., 1994; Michiels and Collard, 1999; Engers et al., 2001). The latter is due to the ability of Rac to upregulate cadherin-dependent adhesion and expression of tissue inhibitor of metalloproteinases (TIMPs). Moreover, increasing Tiam1/Rac signaling by overexpression results in suppression of epithelial invasiveness and reversion of epithelial-mesenchymal transitions in ras-transformed cells (Hordijk et al., 1997), disassembly of cadherin-mediated cell-cell contacts in keratinocytes (Braga et al., 2000), and impairing of migratory behavior of fibroblasts by downregulation of Rho activity (Sander et al., 1999).

Besides cadherins, other receptors have been implicated in the control of cell-cell junctions and the invasive phenotype (Bogenrieder and Herlyn, 2002). Activated leukocyte cell adhesion molecule (ALCAM or CD166) is a novel member of the immunoglobulin superfamily that mediates both heterophilic (ALCAM-CD6) and homophilic (ALCAM-ALCAM) cell-cell interactions (Swart, 2002). ALCAM is ubiquitously expressed in a wide variety of tissues and contributes to growth, development and maintenance of central and peripheral nervous systems (Swart, 2002). ALCAM has been also implicated in the metastatic progression of melanoma, fibrosarcoma and prostate cancer (Degen et al., 1998; van Kempen et al., 2000; Choi et al., 2000; Kristiansen et al., 2003). ALCAM expression correlates with invasiveness of malignant melanoma and is discussed as a prognostic marker in this disease (Degen et al., 1998; van Kempen et al., 2000).

In this study, we show that Tiam1/Rac signaling induces actin-based ALCAM-mediated intercellular adhesion and impairs invasive migration in metastatic melanoma cells.

Summary

Rho-like GTPases such as RhoA, Rac1 and Cdc42 are key regulators of actin-dependent cell functions including cell morphology, adhesion and migration. Tiam1 (T lymphoma invasion and metastasis 1), a guanine nucleotide exchange factor that activates Rac, is an important regulator of cell shape and invasiveness in epithelial cells and fibroblasts. Overexpression of Tiam1 in metastatic melanoma cells converted the constitutive mesenchymal phenotype into an epithelial-like phenotype. This included the induction of stringent cell-cell contacts mediated by the Ig-like receptor ALCAM (activated leukocyte cell adhesion molecule) and actin redistribution to cell-cell junctions. This phenotypic switch was dependent on increased Rac but not Rho activity, and on the redistribution and adhesive function of ALCAM, whereas cadherins were not involved. Although cell proliferation was significantly enhanced, the gain of cell-cell junctions strongly counteracted cell motility and invasion as shown for two- and three-dimensional collagen assays as well as invasion into human skin reconstructs. The reverse transition from mesenchymal invasive to a resident epithelial-like phenotype implicates a role for Tiam1/Rac signaling in the control of cell-cell contacts through a novel ALCAM-mediated mechanism.

Key words: Small GTPase, GEF, Tiam1, Actin cytoskeleton, Cell adhesion, Melanoma, Migration, Invasion
Materials and Methods

Cells and culture conditions

MV3 cells are human melanoma cells. Characteristic of this cell line are markedly tumorigenic properties and an extremely high metastasis rate (van Muijen et al., 1991a). 1F6 is a non-metastatic human melanoma cell line (van Muijen et al., 1991b). MV3, MV3-Tiam1, 1F6 and 1F6-Tiam1 melanoma cells were cultured in DMEM supplemented with 10% fetal calf serum, penicillin and streptomycin. Stable cell lines expressing NH2-terminal-deleted, active C1199-supplemented with 10% fetal calf serum, penicillin and streptomycin. 1F6 and 1F6-Tiam1 melanoma cells were cultured in DMEM (Michiels et al., 1997) were generated by retroviral transduction (Michiels et al., 2000) and selected with neomycin. All cell culture reagents were purchased from Gibco BRL Life Technologies.

Production of GST-PAK-CRIB domain (PAK-CD) and GST-C21 fusion proteins

Cloning of the GST-PAK-CD fusion protein (encompassing amino acids 56-141 from PAK1B), containing the Rac- and Cdc42-binding region from human PAK1B, has been described (Sander et al., 1998). GST-C21 has been described previously (Reid et al., 1996; Reid et al., 1999) and contains the NH2-terminal 90 amino acids, representing the Rho-binding domain, from the Rho effector protein Rhotekin. Expression and purification of recombinant proteins in *Escherichia coli* BL21 cells has been described (Sander et al., 1998).

GTPase activity assays and western blot

The GTPase pull-down assay was carried out essentially as described (Sander et al., 1998; Sander et al., 1999; Reid et al., 1996; Reid et al., 1999). In brief, cell lysates were prepared and incubated with bacterially produced GST-PAK-CD or GST-C21 fusion proteins, bound to glutathione-coupled Sepharose beads. The beads and proteins bound to the fusion proteins were washed in an excess of lysis buffer, eluted in Laemmli sample buffer, and analyzed for bound RhoA or Rac1 molecules by western blot using antibodies against RhoA (mAb 26C4; Santa Cruz Biotechnology) or Rac1 (mAb 23A8; Upstate Biotechnology). The lysates were utilized to examine expression of ALCAM (mAb J4-81, Antigenix America; L50, Sanbio), annexin II and α-catenin (BD Transduction Laboratories).

Immunofluorescence studies

Cells grown on glass cover slips were fixed in 3.7% paraformaldehyde, permeabilized in 0.1% Triton X-100 for 10 minutes, blocked with 2% bovine serum albumin for 1 hour (all reagents were diluted in phosphate-buffered saline), and then incubated with primary antibodies against ALCAM (mAb J4-81, Antigenix America; polyclonal antibody (pAb) N-21, Santa Cruz Biotechnology), E-, M-, N-, P-, R- and VE-cadherin (mAb; BD Transduction Laboratories), Pan-cadherin (mAb; Sigma), Tiam1 (pAb C-16; Santa Cruz Biotechnology), Vinculin (mAb hVIn-1; Sigma), mAbs against annexin II or α-catenin (BD Transduction Laboratories). Antibodies were visualized with Cy5-labeled goat anti-mouse IgG (Dianova) and FITC-labeled goat anti-rabbit IgG (Jackson Immunoresearch Laboratories) as secondary antibodies. Cells were stained simultaneously with TRITC-conjugated phalloidin (Molecular Probes). Images were recorded with a Leica laser-scanning confocal microscopy system TCS-SP2 (Wetzlar).

Spheroid migration assay in three-dimensional (3D) collagen matrices

Spheroids were generated by the liquid overlay technique. 100 mm Petri dishes were coated with aqueous poly-2-hydroxyethyl methacrylate (HEMA, 0.33%; Sigma) solution, dried under sterile conditions, and rinsed with PBS. MV3 and MV3-Tiam1 cells were detached from subconfluent cultures using EDTA (2 mM), washed and added to poly-HEMA-coated petri dishes (0.8×106 cells/ml) and incubated for 48 hours at 37°C in a 5% CO2 atmosphere. Multicellular spheroids developed spontaneously by cell aggregation and clonal growth within clusters. Multicellular spheroids of different sizes were selected using a micropipette under the bright field microscope and incorporated into freshly prepared collagen solution containing native dermal type I collagen (1.67 µg/ml, pH 7.4; Vitrogen, Nutracon). The collagen-containing spheroids spontaneously polymerized after 30 minutes (37°C, 5% CO2).

Video microscopy and computer-assisted cell tracking

Cell migration within 3D collagen lattices was monitored in duplicate experiments by time-lapse digital microscopy using four independent stages, as described (Frield et al., 1997). Computer-assisted cell tracking of 30 randomly selected cells was performed.
The impact of Tiam1 on metastatic melanoma as described (Friedl and Brocker, 2003). In brief, the x- and y-coordinates were collected from the center of the cell with a step interval of 17 minutes and reconstructed either as path at orthotopic position or as migration speed over time for the entire population (Friedl and Brocker, 2003).

**Results and Discussion**

Tiam1 induces homophilic ALCAM-mediated intercellular adhesion

Tiam1 is known to take part in morphological transformation, cell motility and invasive behavior in many cell types, such as T-lymphoma cells, fibroblasts and epithelial cells (Michiels et al., 1995; Hordijk et al., 1997; Sander et al., 1998; Sander et al., 1999). However, the function of the Tiam1/Rac signaling cascade in the cellular invasion and metastasis of human melanoma cells remained unclear. We investigated the consequences of an increased Rac activation in Tiam1-negative melanoma cells by generation of 1F6 (non-metastatic) and MV3 (metastatic) cell lines stably expressing C1199-Tiam1 cDNA employing retroviral transduction (Fig. 1A, upper panel). We found that overexpression of Tiam1 induced an epithelial-like phenotype in the metastatic melanoma cells (Fig. 1B). Whereas Tiam1-negative parental MV3 cells exhibited a fibroblastoid morphology lacking aggregate formation, expression of Tiam1 induced growth in small groups of flat, spread-out cells, as well as strongly adhering aggregates with large cell-cell contact sites. However, Tiam1-expressing non-metastatic 1F6 cells did not show any significant morphological changes (Fig. 1B).

The tumorigenic and metastatic phenotype of melanoma cells often correlates with increased expression of certain cell-cell and cell-matrix adhesion receptors and reduced expression of others (Satyamoorthy et al., 2001), including the functional loss of E-cadherin (Hsu et al., 2000). By contrast, Tiam1 expression is known to promote cadherin-mediated adhesion of fibroblasts and epithelial cells (Hordijk et al., 1997; Sander et al., 1999; Engers et al., 2001). However, we did not detect any expression pattern of the E-, M-, N-, P-, pan-, R- and VE-cadherins either in MV3 or in Tiam1-expressing cells (data not shown). Instead, fluorescence microscopy revealed that localization of the Ig-like receptor ALCAM was remarkably altered in Tiam1-expressing metastatic melanoma cells (Fig. 1C). In MV3-Tiam1 cells, ALCAM was shown to be highly concentrated and accumulated exclusively at cell-cell contact sites colocalizing with filamentous actin and Tiam1. However, in parental MV3 cells, ALCAM lacked membrane staining yet was found diffusely distributed in the cytoplasm and in vesicles (Fig. 1C). By contrast, non-metastatic 1F6 cells constitutively redistributed ALCAM to cell-cell junctions and showed no further change of ALCAM localization under the influence of Tiam1. Thus, the observed cell adhesion seems to be a result of modified homophilic ALCAM-ALCAM interactions in the Tiam1-expressing metastatic cell line, although we cannot exclude the involvement of other Ig- or cadherin-like adhesion receptors.
To examine the assumption of homotypic transcellular adhesion by ALCAM, we used the anti-ALCAM antibody L50 (Sanbio) that has been reported recently to inhibit homophilic ALCAM-ALCAM interactions (van Kempen et al., 2001). As shown in Fig. 2, the well-organized actin cytoskeleton, colocalized with ALCAM clusters at the MV3-Tiam1 cell junctions, are scattered after treatment with L50 antibody. These data proved that ALCAM localization is not the result but the cause of the epithelial-like phenotype. However, the ALCAM staining indicates that it is still at the plasma membrane and is not internalized as found for E-cadherin (Le et al., 1999).

Moreover, overexpression of Tiam1 induced strong Rac activation in both melanoma cell lines whereas Rho activity remained unchanged (Fig. 3A), suggesting that Rac but not Rho controls the phenotypic change. Western blot analysis did not show a quantitative upregulation of ALCAM in Tiam1-expressing cells compared with parental cells (Fig. 1A, lower panel), suggesting that Rac activation in MV3-Tiam1 cells markedly changed the overall surface distribution of ALCAM by inducing ALCAM clustering.

**Rac activation does not affect Rho activity**

It is generally known that Rho GTPases function as critical regulators of actin cytoskeleton remodeling during cell spreading and migration (Ridley, 2001). Ligand-induced activation of Rho stimulates cell contractility and adhesion to the extracellular matrix by induction of stress fiber and focal adhesion complex assembly. By contrast, the activation of Rac enhances cell spreading and migration by stimulating actin polymerization at the plasma membrane and promoting cell migration, which is consistent with the increased spreading and migration observed in Tiam1 cells.

![Fig. 2. Effect of the anti-ALCAM antibody on ALCAM-mediated cell adhesion. Confocal images of the MV3-Tiam1 cell line stained for ALCAM (blue) and F-actin (red). Cells were treated with a monoclonal anti-rabbit IgG (10 μg/ml) as a control (upper panel) or with the anti-ALCAM antibody L50 (10 μg/ml) (lower panel), respectively. Bars, 20 μm.](image1)

![Fig. 3. Interrelation of Rac and Rho activity in Tiam1-expressing melanoma cells. (A) GTPase pull-down assay of parental cells (1F6, MV3) and Tiam1-expressing cells (1F6-Tiam1, MV3-Tiam1). Cell lysates of the indicated cell lines (3×10⁶ cells for Rac assay, 6×10⁶ cells for Rho assay) were incubated with GST-PAK-CD (upper panel) or GST-C21 (lower panel), and bound GTPases were detected by western blot using antibodies against Rac1 and RhoA. (B) Rac and Rho activities were visualized indirectly by staining F-actin (red). Focal adhesion complexes were visualized using anti-vinculin antibody (white). Tiam1 was stained with pAb and FITC-conjugated secondary antibody (green). Note that increased Rac activation did not lead to reduction of stress fiber or focal adhesion formation, indicating a stable level of Rho activity and that Tiam1 colocalizes with F-actin at the cell-cell contact sites in MV3-Tiam1 cells. Bars, 20 μm.](image2)
formation of lamellipodia and membrane ruffles. Several studies have demonstrated that the activity of Rho can be regulated by Rac (van Leeuwen et al., 1997; Kozma et al., 1997; Sander et al., 1999; Zondag et al., 2000; Noren et al., 2001). We therefore examined the impact of Tiam1-mediated Rac activation both on altered Rho activation at the GTPase level and on Rho signaling. As expected, Tiam1 expression induced Rac activation (Fig. 3A, upper panel) and subsequently formation of membrane ruffles and lamellipodia in both melanoma cell lines (Fig. 1B,C and Fig. 3B). Tiam1 was predominantly localized at these sites of increased actin polymerization. However, Tiam1/Rac signaling neither affected the quantity of activated Rho nor the assembly of Rho-derived actin stress fibers and focal adhesions (Fig. 3). As the balance between Rho GTPase activities is a crucial determinant of cellular morphology and migratory behavior of cells, it remains to be explored how the reciprocal activities of Rho GTPases are regulated in melanoma cells.

α-catenin may be the link between F-actin and ALCAM

Our data support current concepts that Tiam1/Rac signaling regulates a coordinated assembly of both actin filaments and cell-cell adhesion (Lozano et al., 2003) and provide insight into a novel ALCAM-mediated mechanism. At this stage, we can only speculate about biochemical pathways linking Rac signaling towards clustered ALCAM molecules. One potential link could be annexin II, which is a phospholipid- and actin-binding protein (Filipenko and Waisman, 2001). Annexin II and ALCAM, both being metastasis-associated proteins (Wu et al., 2002; Degen et al., 1998), synergistically contribute to the metastatic progression of fibrosarcoma cells (Choi et al., 2001). Moreover, annexin II has been shown to be a binding partner of a 16 S Rac complex that localizes rapidly to cell-cell contact sites (Hansen et al., 2002). As shown in Fig. 4A, the Tiam1-expressing MV3 cell line seems to express a slightly higher level of annexin II that is however predominantly detected in the nuclei of both cell lines MV3-Tiam1 (Fig. 4B) and MV3 (data not shown). Studies of the functional localization of annexin II have shown increased accumulation of tyrosine-phosphorylated annexin II within the nuclei of keratinocytes, HeLa cells and v-Src-transformed fibroblasts, respectively (Kim et al., 1998; Chiang et al., 1996; Eberhard et al., 2001). Although its nuclear function is not understood, its absence from cell-cell contacts makes its contribution to the phenotypic reversion unlikely. The 34 kDa protein band, which has been detected by immunoblotting in the lysate of the Tiam1-expressing MV3 cells (Fig. 4A), might be related to the proteolytic cleavage of annexin II that has been recently shown to abolish annexin II binding to the plasma membrane (Babiychuk et al., 2002).

Our data on Tiam1/Rac-induced ALCAM-mediated adhesion at the cell-cell junction (Fig. 1C) strongly support the notion that activation of ALCAM-mediated adhesion is dynamically regulated through reorganization of the actin cytoskeleton (Nelissen et al., 2000). ALCAM, similar to integrins and cadherins, exhibits putative binding sites to intracellular cytoskeletal and adaptor proteins, including members of the ERM family (Sechi and Wehland, 2000) and α-catenin (Fukata and Kaibuchi, 2001), which directly bind positively charged and clustered residues in cytoplasmic receptor tails. This region comprises a short 32 amino acid intracellular tail with 8 lysines and 2 histidines on ALCAM molecules (Tanaka et al., 1991). Expression of α-catenin was demonstrated to be associated with melanoma invasiveness and metastasis (Zhang and Hersey, 1999). Moreover, α-catenin, which is an essential element of the E-cadherin invasion suppressor complex, has indeed been shown to affect ALCAM localization to cell-cell contact sites in prostate cancer cells (Tomita et al., 2000). In this regard, we examined both expression and cellular localization of α-catenin in the respective melanoma cells. As shown in Fig. 4A, α-catenin is similarly expressed in 1F6 and MV3 cell lines independent of Tiam1 expression. Notably, a colocalization of α-catenin was observed in MV3-Tiam1 cells with both ALCAM and filamentous actin (Fig. 4C). Thus, it is tempting to speculate...
Tiam1 inhibits melanoma motility and invasion.

Migration is a multistep process that requires changes in cell polarity, cell-cell and cell-substrate adhesion driven by dynamic assembly and the reorganization of the actin cytoskeleton (Friedl and Wolf, 2003). The GTPases of the Rho family regulate actin dynamics by diverse mechanisms (Hall, 1998; Mackay and Hall, 1998) and contribute to tumor cell invasion (transcellular migration) and metastasis (Hernandez-Alcoceba et al., 2000; Schmitz et al., 2000; Price and Collard, 2001; Jaffe and Hall, 2002; Sahai and Marshall, 2002). Therefore, we next investigated the impact of Tiam1-induced Rac activation on melanoma migration and invasiveness using different models. To study the haptokinetic migration across a 2D substrate, scratch wound assays in confluent monolayers of melanoma cells were performed. During a period of 7 hours, cells moved forward and closed the gap independently of cell division (data not shown). The expression of Tiam1 in MV3 cells resulted in a strong inhibition of migration in metastatic cells compared with MV3 control cells (Fig. 6A). As 1F6-Tiam1 cells showed a migration rate that was comparable with the parental 1F6 cells, we conclude that increased Rac activity does not significantly influence the migratory properties of non-metastatic melanoma cells.

To explore further whether Tiam1-reduced motility also implies reduced invasion in more complex models, we employed human skin reconstructs (i.e. a 3D in vitro dermoeipidermal tissue consisting of multilayered keratinocytes on fibroblast-conditioned and -contracted collagen gels; Meier et al., 2000). As shown in Fig. 6B (upper panel), the metastatic MV3 cells exhibited invasive growth of tumor cell strata into the deeper dermis. Furthermore, a few proliferating MV3 cells were observed within a band-like tumor cell aggregate at the epidermal-dermal junction. By contrast, MV3-Tiam1 melanoma cells proliferated extensively and formed giant tumor masses at the epidermal-dermal junction and in the upper dermis; however, they lacked the invasive capacity of the parental cells (Fig. 6B, lower panel). The different cell morphology and position of the respective cell lines is shown at higher magnification (Fig. 6C). MV3-Tiam1 cells adhered to each other, forming confluent spheroid tumor cell nests and clusters.

To test whether the alterations in dermal invasion patterns were reflected by actual changes in cell migration caused by adhesive cell-cell junctions, the effect of Tiam1 on MV3 migration was assessed by time-lapse videomicroscopy and quantitative analysis, using spheroid invasion in 3D collagen matrices. Whereas MV3 cells rapidly polarized and detached for migration of single cells into the adjacent collagen lattice (Fig. 6D, left panel), overexpression of Tiam1 resulted in marked cell retention towards the spheroid and a near-total abrogation of migration (Fig. 6D, right panel). Consequently, the resulting lengths of the cell paths as well as the related population speed of migration obtained from single cell tracking were significantly reduced in Tiam1-expressing cells compared with control cells (Fig. 6D, lower panel). Because the capacity to interact with the collagen substrate and to generate outward polarization remained unaffected, the mechanism of impaired migration resided in the increase of cell-cell adhesion and cell retention within the conglomerate.

It has been shown that activation of Rac results in E-cadherin-mediated cell-cell adhesion and, subsequently,
The impact of Tiam1 on metastatic melanoma inhibits migration and invasion of epithelial cells (Braga et al., 1997; Hordijk et al., 1997; Takaishi et al., 1997; Engers et al., 2001). In addition to induced cell adhesion, the inhibition of invasion of renal cell carcinomas was shown to be promoted by transcriptional upregulation of TIMP1 and TIMP2 (Engers et al., 2001). We examined all four TIMP proteins in cells and in medium but did not find any difference in their expression patterns, neither in parental cells nor in Tiam1-expressing melanoma cell lines (data not shown). By contrast, sustained Rac activation is sufficient to destabilize cadherin-mediated cell-cell contacts in keratinocytes (Braga et al., 2000; Braga, 2000) and to induce invasion and metastasis of murine T-lymphoma cells (Habets et al., 1994; Michiels et al., 1995). Our data instead demonstrate the inhibitory regulation of 2D and 3D cell motility and invasion of metastatic melanoma by overexpression of Tiam1, which is based on triggering intercellular adhesion not by cadherins but by ALCAM.

Fig. 6. The impact of Tiam1 expression on MV3 melanoma migration. (A) Wound closure in a 2D cell motility assay. Closure of a scratch wound in a confluent monolayer of cells was monitored over a period of at least 7 hours. Tiam1 expression strongly inhibited migration of the metastatic MV3-Tiam1 cells (filled circles) compared with the parental cell line MV3 (open circles). The migration potential of non-metastatic cells 1F6 (open triangles) and 1F6-Tiam1 (filled triangles) was not significantly altered in the 2D system. A slight inhibition of migration was detectable. (B) Characterization of MV3 and MV3-Tiam1 cells in human skin reconsticts. Upper panel: MV3 melanoma cells form band-like tumor cell aggregates at the epidermal-dermal junction and exhibit invasive tumor growth of tumor cell strands into the deeper dermis (arrows). Lower panel: MV3-Tiam1 melanoma cells display a high proliferation rate (red) and form giant tumor masses at the epidermal-dermal junction and in the upper dermis; stained with Ki 67 (red), ×50. (C) Magnified zones (tetragons) highlight the different cell morphology and position in greater detail. (D) Reinforced cell-cell adhesions and impaired migration after expression of Tiam1. Multicellular spheroids of MV3 control cells (left panel) or Tiam1-expressing MV3 cells (right panel) were incorporated into 3D collagen lattices and monitored by time-lapse videomicroscopy. Paths of individual cells and resulting migration speed were obtained from single cell tracking (after 11 hours). Upon long-term observation, stringent cell-cell junctions preventing cell detachment in Tiam1-positive cells were retained for up to 72 hours (not shown). Bar, 0.6 mm.

Conclusions
In the present study we have shown that overexpression of the RacGEF Tiam1 results in an epithelial-like phenotype only in the invasive melanoma cell line MV3. We observed that sustained Rac activation induced a novel type of intercellular adhesion, possibly by actin-cytoskeleton-derived ALCAM clustering, and also inhibited migratory processes required for melanoma invasion. Our data imply that ALCAM-mediated cell-cell contacts are most likely responsible for the inhibitory regulation of cell migration. Moreover, the significant increase in cell proliferation supports the idea that Ras and Rac signaling pathways probably respond synergistically to melanoma progression. An important question that remains unclear is why Tiam1 affects the metastatic but not the non-metastatic cells. However, it is well documented that adhesion receptors fulfill distinct biological functions during subsequent stages of melanoma progression (Bogenrieder and Herlyn,


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