The integrin $\alpha v \beta 6$ is critical for keratinocyte migration on both its known ligand, fibronectin, and on vitronectin

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SUMMARY

The integrin $\alpha v \beta 6$ is expressed on a variety of epithelial cells during dynamic processes including organogenesis, tissue injury and malignant transformation. However, because of the lack of tools to specifically inhibit the function of this integrin, little is known about its effects on cell behavior. To directly examine the role of this integrin in cell migration, we used keratinocytes derived from wild-type mice or mice expressing a null mutation in the $\beta 6$ subunit ($\beta 6^{-/-}$) to perform migration assays in vitro. Migration on the known $\alpha v \beta 6$ ligand, fibronectin, was reduced in keratinocytes from $\beta 6^{-/-}$ mice. Interestingly, keratinocytes from $\beta 6^{-/-}$ mice also demonstrated markedly reduced migration on vitronectin, a protein not previously known to be a ligand for $\alpha v \beta 6$. An anti-$\alpha v \beta 6$ monoclonal antibody 10D5, generated by immunization of $\beta 6^{-/-}$ mice with murine keratinocytes, inhibited adhesion and migration of wild-type keratinocyte on both vitronectin and fibronectin to levels similar to those seen with keratinocytes from $\beta 6^{-/-}$ mice. $\alpha v \beta 6$-mediated migration on both ligands was dramatically augmented by treatment with phorbol myristate acetate (PMA) or with hepatocyte growth factor, and augmentation of migration by either stimulus could be abolished by the PKC inhibitor GF109203X, suggesting a critical role for PKC in enhancement of $\alpha v \beta 6$-mediated cell migration.

Key words: Migration, Keratinocyte, Integrin, $\alpha v \beta 6$, Fibronectin, Vitronectin, Hepatocyte growth factor, Protein kinase C

INTRODUCTION

Integrins are heterodimeric receptors for extracellular matrix and cell surface counterreceptors, which play important roles in embryonic development, inflammation, wound healing, and tumorigenesis (Hynes, 1987; Ruoslahti and Pierschbacher, 1987). $\alpha v$ integrins ($\alpha v \beta 1$, $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha v \beta 6$ and $\alpha v \beta 8$) mediate cell adhesion to various matrix proteins including fibronectin, vitronectin, tenascin, osteopontin and fibrinogen at sites containing the tri-peptide sequence arginine-glycine-aspartic acid (RGD). Although the first-described member of this sub-family, $\alpha v \beta 3$, appears to bind to virtually all of these proteins, the other $\alpha v$-integrins are more restrictive in their interactions with ligands. For example, $\alpha v \beta 5$ (Smith et al., 1990) and $\alpha v \beta 8$ (Nishimura et al., 1994) have been reported to be principally vitronectin receptors, and $\alpha v \beta 6$ has been reported to principally bind fibronectin and, to a lesser extent, tenascin (Busk et al., 1992; Weinacker et al., 1994; Prieto et al., 1993; Yokosaki et al., 1996).

In addition to recognizing distinct subsets of RGD-containing ligands, $\alpha v$-integrins exert distinct effects on cell behavior. For example, $\alpha v \beta 5$ has been reported to play a unique role in activation-dependent cell migration (Klemke et al., 1994), and $\alpha v \beta 6$ plays a unique role in modulating local inflammatory response in the lungs and skin (Huang et al., 1996). We and others have reported that $\alpha v \beta 6$ is preferentially expressed on cells at the leading edge of healing cutaneous wounds and at the interface between tumor cells and the adjacent stroma (Haapasalmi et al., 1996; Breuss et al., 1995). When cells expressing this receptor are plated on the known ligand, fibronectin, $\alpha v \beta 6$ rapidly accumulates at points of initial contact, and then rapidly redistributes to the leading edge of migrating cells (R. Pytela, personal communication). Together, these observations suggested that $\alpha v \beta 6$ might also be important in cell migration. However, since no specific blocking agents directed at $\alpha v \beta 6$ had been described previously, any role for $\alpha v \beta 6$ in cell migration could not be directly examined.

In the present study, we utilized keratinocytes cultured from mice we have generated expressing a null mutation in the $\beta 6$ subunit to directly examine the role of this integrin in keratinocyte migration. By immunizing these mice with murine keratinocytes, we were able to generate the first function-blocking monoclonal antibody against $\alpha v \beta 6$ and used this antibody to confirm that results obtained with cells from $\beta 6^{-/-}$ mice were not due to compensatory responses to the null mutation. The results of these studies demonstrate a critical role for $\alpha v \beta 6$ in cell migration both on its known ligand, fibronectin, and on vitronectin, a protein that has not been previously identified to be a ligand for $\alpha v \beta 6$. 
MATERIALS AND METHODS

Cells, cell culture and reagents
Monoclonal antibodies CSβ6 and 10D5 against the integrin αβ6 were prepared in our laboratory as described below. Mouse monoclonal antibodies P1F6 and P5D2, directed against human β5 and β1, were gifts from Elizabeth Wayner (University of Minnesota, Minneapolis, MN), and were prepared in our laboratory from hybridoma lines as previously described (Weinacker et al., 1994). Murine keratinocytes were obtained and grown in keratinocyte growth medium (KGM, Clonetics, San Diego, CA) as previously described (Huang, 1996). Briefly, mouse skin was kept in 0.1% bacterial protease (P8811, Sigma, St Louis, MO) overnight at 4°C. The following day the epithelial layer was scraped off and incubated in 0.05% trypsin for 40 minutes at 37°C. The cells were disaggregated by pipetting, washed twice with PBS, resuspended in KGM and plated onto dishes coated with collagen. SW480 cells stably transfected with the presence or absence of phosphoryl myristate acetate (PMA, 10 ng/ml) or growth factors. For inhibition experiments, antibody 10D5 (10 μg/ml) was added into upper and lower chambers. To evaluate the role of protein kinase C (PKC) on migration, keratinocytes were treated with the PKC inhibitor bisindolylmaleimide I (GF 109203X, Calbiochem, San Diego, CA) at 37°C for 30 minutes before addition of PMA or growth factors. After a 6 hour incubation, cells were fixed with 2% paraformaldehyde and stained with 0.5% crystal violet in 1% formaldehyde. Cells in the upper chamber were removed and cells on the lower surface were counted with a ×10 grid at high power magnification (×40). Multiple fields were counted and averaged for each condition studied. The data represent at least three individual experiments.

Cell adhesion assay
96-well non-tissue culture treated polystyrene multiwell microtiter plates (Linbro/Titertek, Flow Laboratories, Mclean, VA) were coated with vitronectin, fibronectin or collagen. A 100 μl solution containing various amounts of matrix was added to the wells and incubated at 37°C for 1 hour. After incubation, wells were washed with PBS, then blocked with 1% BSA in serum-free DMEM at 37°C for 30 minutes. Control wells were incubated with 1% BSA in DMEM. Cells were harvested in the same way as for the migration assay and resuspended in serum-free KGM, and then added to each protein-coated well in the presence or absence of PMA. For blocking experiments, cells were incubated with antibodies for 15 minutes at 4°C before plating. The plates were centrifuged (top side up) at 10 g for 5 minutes before incubation for 1 hour at 34°C in humidified 7% CO2. Non-adherent cells were removed by centrifugation top side down at 48 g for 5 minutes. The attached cells were fixed with 1% formaldehyde and stained with 0.5% Crystal Violet, then the wells were washed with PBS. The relative number of cells in each well was evaluated by measuring the absorbance at 595 nm in a Microplate Reader (Bio-Rad). The data represent at least three individual experiments.

Statistical analysis
Data are expressed as the mean ± s.e.m. of a given number of observations. Comparisons between two normally distributed groups were made using an unpaired Student’s t-test. Where appropriate one way analysis of variance (ANOVA) was used to compare multiple groups. A P value of <0.05 was considered to be significant.

RESULTS

Development and characterization of monoclonal antibodies
To generate antibodies against murine αvβ6, secreted human αvβ6 and murine keratinocyes were used as immunogens in mixed 129/C57BL6 background β6−/− mice. Supernatants from the hybridomas generated were screened for differential staining of mock- and β6-transfected SW480 cells. The resulting antibodies CSβ6 and 10D5 stained both human β6 expressed on SW480 cells and mouse β6 on wild-type keratinocytes (Fig. 1A). Specificity for αvβ6 was confirmed by the lack of staining of mock-transfected SW480 cells which we have previously shown express several β1-containing integrins and αvβ5 (Weinacker et al., 1994). As shown in Fig. 1A, mock-transfected cells express large amounts of αvβ5 (detected by monoclonal antibody P1F6) and large amounts of β1-integrins

Flow cytometry
Cultured cells were harvested by trypsinization and washed twice with PBS. Non-specific binding was blocked with normal goat serum at 3°C for 10 minutes. Cells were then incubated with primary antibodies for 20 minutes at 4°C, followed by secondary antibodies conjugated with phycoerythrin (Boehringer Mannheim, Indianapolis IN). Between incubations, cells were washed twice with PBS. Stained cells were resuspended in 100 μl of PBS and analyzed by Becton Dickinson FACSsort.

Immunoprecipitation
Murine keratinocytes were labeled with 0.5 mCi [35 S]methionine overnight in methionine-free DME supplemented with 1% fetal bovine serum, 2% KGM, penicillin/streptomycin and lyzed in immunoprecipitation buffer (20 mM Tris-HCl, pH 7.5, 1% Triton X-100, 100 mM NaCl, 1 mM CaCl2, 1 mM MgCl2). Lysates were pre-cleared with Protein A-Sepharose, incubated with primary antibody overnight at 4°C, followed by rabbit anti-mouse IgG Fc (Pierce, Rockford IL) for an additional 30 minutes. Immune complexes were captured by 40 minutes incubation with Protein A-Sepharose. Samples were separated by SDS-PAGE on 7.5% acrylamide gels. Gels were impregnated with 2.5-diphenylxazole (PPO, Fisher Scientific) and exposed to film at −80°C.

Migration assay
Cell migration assays were performed with matrix coated transwell plates (8 μm pore size, Costar, Cambridge, MA). The under surface of the membrane was coated with collagen (10 μg/ml), fibronectin (10 μg/ml) or vitronectin (10 μg/ml) in PBS for 1 hour at 37°C and blocked with 1% BSA. Primary cultured keratinocytes were harvested with trypsin/EDTA and trypsin was inactivated with soybean trypsin inhibitor. Cells were suspended in serum-free KGM and plated in the upper chamber at a density of 3.6×10⁵ per well in 100 μl medium in the presence or absence of phosphoryl myristate acetate (PMA, 10 ng/ml) or growth factors. For inhibition experiments, antibody 10D5 (10 μg/ml) was added into upper and lower chambers. To evaluate the role of protein kinase C (PKC) on migration, keratinocytes were treated with the PKC inhibitor bisindolylmaleimide I (GF 109203X, Calbiochem, San Diego, CA) at 37°C for 30 minutes before addition of PMA or growth factors. After a 6 hour incubation, cells were fixed with 2% paraformaldehyde and stained with 0.5% crystal violet in 1% formaldehyde. Cells in the upper chamber were removed and cells on the lower surface were counted with a ×10 grid at high power magnification (×40). Multiple fields were counted and averaged for each condition studied. The data represent at least three individual experiments.
αβ6 mediates cell migration and vitronectin cell migration

Preliminary studies also showed that keratinocyte migration on vitronectin and fibronectin was greatly augmented by PMA. Keratinocytes from wild-type and β6−/− mice migrated equally well on collagen-coated membranes (Fig. 2A). Migration of keratinocytes from β6−/− mice on fibronectin-coated membranes was decreased by approximately 60% compared with migration of cells from wild-type mice, and migration of keratinocytes from wild-type mice was decreased to the same extent by antibody 10D5 (Fig. 2A). The effects of inactivation of the β6 gene and of 10D5 were even more dramatic with respect to migration on vitronectin and, again, the reduction in migration was similar for cells from β6−/− mice and cells from wild-type mice in the presence of 10D5. These data suggest that αβ6 plays an important role in keratinocyte migration on fibronectin and is critical for migration on vitronectin. The finding that cells from β6−/− mice and cells from wild-type mice incubated with 10D5 behaved in identical fashion on both matrix proteins confirms that inhibition of migration of β6−/− cells was specifically due to the loss of αβ6 rather than some other compensatory response to in vivo inactivation of this integrin. The residual migration on
fibronectin seen in cells from \( \beta 6^{+/+} \) mice suggests that other receptors (e.g. \( \alpha 5 \beta 1 \)) also contribute to keratinocyte migration on this ligand.

\( \alpha \nu \beta 6 \) mediates cell attachment to vitronectin

Cell migration involves attachment and detachment to the underlying matrix. To determine whether decreased cell migration of \( \beta 6^{-/-} \) keratinocytes was associated with a quantitative change in cell adhesion to vitronectin and/or fibronectin, we performed cell adhesion assays. Cells were plated in wells coated with fibronectin, vitronectin or collagen. \( \beta 6^{-/-} \) cells showed decreased adhesion to both vitronectin and fibronectin (Fig. 2B). Adhesion to collagen, an extracellular matrix protein that is not a ligand for \( \alpha \nu \beta 6 \), was similar for both types of cells. The addition of PMA did not alter adhesion under any of the above conditions (data not shown). The role for the integrin \( \alpha \nu \beta 6 \) in mediating adhesion of murine keratinocytes to fibronectin and vitronectin was further confirmed with the \( \alpha \nu \beta 6 \) blocking antibody 10D5 (Fig. 2B). Again, 10D5 inhibited adhesion of wild-type keratinocytes to both fibronectin and vitronectin to the same level seen in \( \beta 6^{-/-} \) keratinocytes.

\( \alpha \nu \beta 6 \)-mediated migration on vitronectin and fibronectin is greatly enhanced by activation of protein kinase C

Previous studies have suggested that integrin-mediated cell migration can be enhanced by activation of protein kinase C (PKC). In the most dramatic example of this effect, \( \alpha \nu \beta 5 \)-mediated migration of the pancreatic carcinoma cell line, FG, was shown to absolutely require activation of this pathway (Klemke et al., 1994). To determine the role of PKC-dependent pathways in \( \alpha \nu \beta 6 \)-mediated cell migration, we examined the effects of PMA, an activator of several isozymes of PKC, on the migration of wild-type and \( \beta 6^{-/-} \) keratinocytes. Migration of wild-type keratinocytes on both fibronectin and vitronectin was significantly increased by PMA (Fig. 3B,C). Migration of \( \beta 6^{-/-} \) keratinocytes on vitronectin remained minimal even after treatment with PMA, suggesting that \( \alpha \nu \beta 6 \) is the principal receptor responsible for PMA-induced migration on vitronectin in these cells. Migration of \( \beta 6^{-/-} \) keratinocytes was

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**Fig. 2.** (A) Role of \( \alpha \nu \beta 6 \) in cell migration. Keratinocytes from wild-type (Wt) and \( \beta 6^{-/-} \) mice were plated on transwell membranes coated with collagen, fibronectin or vitronectin in the presence of PMA. Wild-type keratinocytes were plated in the presence or absence of the \( \alpha \nu \beta 6 \) blocking monoclonal antibody, 10D5. Cells migrating onto the bottom side of the membrane were stained and counted under microscopy at \( \times 40 \). The data calculated from three fields of three individual experiments are expressed as the mean (± s.e.m.). Significantly less than wild type, \( *P<0.01, \quad **P<0.001 \).

(B) Role of \( \alpha \nu \beta 6 \) in cell adhesion. Keratinocytes from wild-type and \( \beta 6^{-/-} \) mice were plated on 96-well plates coated with collagen, fibronectin or vitronectin. Wild-type cells were plated in the presence or absence of monoclonal antibody 10D5. Cells were allowed to attach to the matrix for one hour, then fixed and stained. Adhesion was expressed as absorbance at 595 nm. Data calculated from triplicate wells of three individual experiments are expressed as the mean (± s.e.m.). Significantly less than wild type, \( *P<0.05, \quad **P<0.001 \).

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**Fig. 3.** Effects of PMA on migration of murine keratinocytes. Confluent keratinocytes from \( \beta 6^{-/-} \) or wild-type mice were plated on transwell membranes coated with collagen (A), fibronectin (B) or vitronectin (C) at a concentration of 10 \( \mu \text{g/ml} \) in the presence or absence of PMA. Cells migrating onto the bottom side of the membrane were stained and counted by light microscopy at \( \times 40 \). The data calculated from three fields of five individual experiments are expressed as the mean (± s.e.m.). *Significantly less than \( \beta 6^{+/+} \), \( P<0.001 \).
augmented by PMA, but remained significantly reduced compared to migration of PMA-treated wild-type cells.

To confirm that augmentation of αvβ6-mediated migration by PMA was due to activation of protein kinase C, we next determined whether the protein kinase C inhibitor, GF 109203X, could prevent the PMA-induced augmentation of keratinocyte migration. As shown in Fig. 4, GF 109203X significantly inhibited the PMA-induced augmentation of migration, with complete inhibition at a concentration of 2 μM.

**Hepatocyte growth factor increased αvβ6-mediated migration of murine keratinocytes on fibronectin and vitronectin through a pathway involving protein kinase C**

In human pancreatic carcinoma (FG) cells, in addition to the artificial effects of PMA, PKC-mediated enhancement of migration could be induced by EGF and IGF-1. Because of the dramatic effects of PMA on αvβ6-mediated keratinocyte migration, we suspected that a similar pathway would play a prominent role in αvβ6-mediated migration. To determine whether such a response could be induced by biologically relevant stimuli in these cells, we examined the effects of 4 different growth factors, EGF, IGF-1, KGF and HGF on the migration of wild-type murine keratinocytes on collagen, fibronectin and vitronectin. These growth factors were selected because each is known to have significant biological effects on epithelial cells. As shown in Fig. 5, there were no consistent effects of any of these growth factors on migration on collagen. Neither EGF nor IGF-1 increased migration on fibronectin or vitronectin, but migration on both matrix proteins was significantly enhanced by both HGF and KGF, with the largest effect produced by HGF at a concentration of 5 ng/ml. Higher concentrations of HGF and especially KGF induced smaller or insignificant effects on migration.

To determine the roles of αvβ6 and of a PKC-dependent pathway in the HGF-induced enhancement of keratinocyte migration, we examined the effects of the optimal concentration of GF109203X and of the αvβ6-blocking antibody 10D5 on migration of wild-type and β6−/− keratinocytes (Fig. 6). Again, there was little effect of HGF, GF1092903X or 10D5 on migration of either type of keratinocyte on collagen, but the HGF-induced augmentation of migration of wild-type keratinocytes on either fibronectin or vitronectin was prevented by addition of the αvβ-blocking antibody or the PKC inhibitor. HGF did significantly increase migration of β6−/− keratinocytes on fibronectin, but this effect...
of PMA, αvβ6-mediated migration was dramatically augmented by hepatocyte growth factor, a stimulus with potential biological significance. The HGF-mediated enhancement of migration also appeared to require PKC, since it could be abolished by the PKC inhibitor GF 109203X.

At least one previous study has examined the roles of integrins in keratinocyte migration on vitronectin (Kim et al., 1994). In that study, the authors demonstrated that the addition of vitronectin to glass coverslips enhanced keratinocyte migration, and that this effect could be reduced by two different antibodies against αvβ5 or by an RGD-containing peptide. They further showed by vitronectin affinity chromatography, immunoprecipitation and flow cytometry that the cells expressed the integrin αvβ5, but not αvβ3. That study differed from the present study in several respects. First, migration was assessed over higher concentrations of vitronectin, ranging from 20 to 150 μg/ml, with the most significant increases in migration occurring at concentrations above 40 μg/ml. Second, the authors only examined migration of unstimulated cells, an effect that is quite small compared to migration of keratinocytes on vitronectin after stimulation with PMA or growth factors. Finally, the authors did not have any reagents to allow them to evaluate any possible contribution of αvβ5 to keratinocyte migration, since there is no blocking antibody available against murine αvβ5. Based on our own observations with keratinocytes from mice we have recently generated expressing a null mutation in the β5 subunit, it is likely that αvβ5 does contribute to PMA-induced keratinocyte migration over vitronectin, but its role is minor compared to the role of αvβ6 (unpublished observations).

There are currently no good reagents for quantifying surface expression of αvβ5 on murine cells. It is therefore not possible for us to be certain that the level of αvβ5 expression was not altered by inactivation of the β6 subunit gene. However, if such a compensatory change did occur, one would expect β6 inactivation to result in an increase in surface expression of αvβ5. Such an effect would not be expected to result in a decrease in cell adhesion to vitronectin, as seen in the current study. Furthermore, the fact that keratinocyte migration and adhesion to vitronectin was also inhibited by a monoclonal antibody that specifically recognizes αvβ6 and not αvβ5, makes any compensatory responses to gene inactivation unlikely as an explanation for our findings.

Previous studies, principally utilizing the human pancreatic carcinoma cell line, FG, have demonstrated a central role for the integrin αvβ6 in migration on vitronectin. In those studies, αvβ5-mediated migration, like the αvβ6-mediated migration we describe in the current study, was dramatically dependent on activation of PKC (Klemke et al., 1994; Yebra et al., 1995, 1996). In addition to PMA, PKC-dependent activation of migration could be induced by the growth factor–receptor agonists, EGF or IGF-1. In the current study, utilizing murine keratinocytes, αvβ6-mediated migration was activated by HGF, and to a lesser extent by KGF, but not by EGF or IGF-1. However, like the effects of EGF and IGF-1 on αvβ5-mediated migration of FG cells, the effects of HGF on αvβ6-mediated migration appeared to involve a PKC-dependent pathway. In order to maintain primary cultures of murine keratinocytes, it is necessary to add low concentrations of both

**DISCUSSION**

In this study, the use of keratinocytes from mice deficient in the β6 subunit and of the αvβ6-blocking antibody 10D5 revealed a critical role for the integrin αvβ6 in keratinocyte migration over both it’s known ligand, fibronectin, and a previously unrecognized ligand, vitronectin. That vitronectin is indeed a ligand for αvβ6 was confirmed by impaired adhesion of β6-/- keratinocytes to vitronectin and a similar effect of 10D5 on adhesion of wild-type keratinocytes. As has previously been described for αvβ5-mediated migration, αvβ6-mediated migration was dramatically augmented by PMA, strongly suggesting a role for a pathway involving protein kinase C. In addition to the somewhat artificial effects
EGF and insulin to the medium. It is thus possible that addition of EGF and IGF-1 failed to enhance migration in these cells because they had already become adapted to these growth factors. Alternatively, the signaling pathways linking specific growth factor receptors to PKC activation and enhancement of integrin-mediated migration may differ in FG cells and murine keratinocytes. Finally, it is possible that the signaling pathways linking specific growth factor receptors to \( \alpha \beta^5 \) or \( \alpha \beta^6 \)-mediated migration may be different.

At least one previous report suggested that keratinocyte migration on fibronectin is principally mediated by the integrin \( \alpha \delta \beta^1 \), based on the observation that migration was largely inhibited by an antibody to this integrin (Lange et al., 1995). Again, the role of \( \alpha \beta^6 \) could not be examined because of the lack of blocking reagents. Our finding that murine keratinocytes are still able to migrate on fibronectin (albeit significantly less well) in the absence of \( \alpha \beta^6 \) suggests that another integrin may also participate in this process.

HGF has been shown to have a broad spectrum of activities, including enhancement of motility in several different types of cells (Sugawara et al., 1997; Dignass and Podolsky, 1994; Weidner et al., 1990; Weimar et al., 1997). In this study, we show that one mechanism for enhancement of motility is augmentation of integrin-mediated migration. As has previously been described for augmentation of \( \alpha \beta^5 \)-mediated migration in FG cells, this effect of HGF does not appear to equally enhance all integrin-mediated migration, since migration on collagen, a process that presumably requires the participation of a different integrin or integrins, was largely unaffected by HGF.

In summary, we have demonstrated a critical role for the integrin \( \alpha \beta^6 \) in keratinocyte migration on both the known ligand, fibronectin, and a previously unrecognized ligand, vitronectin. Activation of \( \alpha \beta^6 \)-mediated migration appears to be central to the enhancement of migration of these cells over either ligand in response to hepatocyte growth factor, through a pathway that involves protein kinase C. In addition, we describe the development of the first \( \alpha \beta^6 \)-blocking antibody, a tool that should be useful for examining possible roles of this integrin in a variety of other biological processes.

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