The Met Receptor and $\alpha_6\beta_4$ Integrin Can Function Independently to Promote Carcinoma Invasion*

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It has been proposed that a constitutive, physical association of the Met receptor and the $\alpha_6\beta_4$ integrin exists on the surface of invasive carcinoma cells and that hepatocyte growth factor (HGF)-mediated invasion is dependent on $\alpha_6\beta_4$ (Trusolino, L., Bertotti, A., and Comoglio, P. M. (2001) Cell 107, 643–654). The potential significance of these results prompted us to re-examine this hypothesis. Using three different carcinoma cell lines that express both Met and $\alpha_6\beta_4$, we were unable to detect the constitutive association of these receptors by co-immunoprecipitation. Moreover, carcinoma cells that lacked expression of $\alpha_6\beta_4$ exhibited Met-dependent invasion toward HGF, and increasing Met expression by viral infection of these cells enhanced invasion without inducing $\alpha_6\beta_4$ expression. Although expression of $\alpha_6\beta_4$ in such cells enhanced their invasion to HGF, it also enhanced their ability to invade toward other chemotactants such as lysophosphatidic acid, and this latter invasion was not inhibited by a function-blocking Met antibody. Finally, depletion of $\beta_4$ by RNA interference in invasive carcinoma cells that express both receptors reduced the ability of these cells to invade toward HGF by $\sim 25\%$, but it did not abrogate their invasion. These data argue that the invasive function of Met can be independent of $\alpha_6\beta_4$ and that $\alpha_6\beta_4$ has a generic influence on the invasion of carcinoma cells that is not specific to Met.

Understanding the receptor-mediated mechanisms that underlie invasive carcinoma is a timely and significant endeavor. The involvement of specific integrins and growth factor receptors in the invasive process is established, and several lines of evidence indicate that these two classes of surface receptors may cooperate to effect a wide range of biological functions, including the migration and invasion of tumor cells (2–4). The available data indicate that integrin and growth factor signaling can be synergistic, and in some cases physical association may occur between these receptor types. Insight into the nature of such receptor interactions has important implications not only for understanding the biology of tumor invasion but also for the design and use of therapeutics targeted to these receptors (5).

An integrin of particular relevance to invasive carcinoma is $\alpha_6\beta_4$ (6–9). This integrin, which is expressed primarily on the basal surface of most epithelia and in most carcinoma cells, is defined as an adhesion receptor for most of the known basement membrane laminins (6, 9). A primary function of $\alpha_6\beta_4$, revealed by studies of knock-out mice, is to maintain the integrity of epithelia (10, 11). This critical role for $\alpha_6\beta_4$ derives from its ability to mediate the formation of stable adhesive structures, termed hemidesmosomes, on the basal cell surface that link the cytoskeleton network with lamins in the basement membrane (12). Recent studies have revealed novel and important functions for this integrin in the migration and invasion of carcinoma cells (13). The expression of $\alpha_6\beta_4$ is maintained or often increased in invasive and metastatic carcinomas, and its expression level correlates with the progression of these carcinomas (14). More recently, compelling data were reported that suggest the $\alpha_6\beta_4$ integrin is essential for squamous carcinogenesis (15).

Given the potential importance of the $\alpha_6\beta_4$ integrin to invasive carcinoma, extensive efforts are being made to define the mechanisms by which it facilitates the invasive process. Advances include the observation that $\alpha_6\beta_4$ is localized to the leading edge of migrating carcinoma cells where it can contribute to the formation and stabilization of actin protrusions (16, 17). In addition, there is evidence from several laboratories indicating that $\alpha_6\beta_4$ stimulates the activity of phosphoinositide 3-OH kinase (PI3K) in invasive carcinoma cells and that PI3K is essential for migration and invasion (7, 18). Interestingly, it has been suggested that $\alpha_6\beta_4$ activates PI3K and mediates invasion through its ability to cooperate with specific growth factor receptors (1, 4, 18). For example, $\alpha_6\beta_4$ has been shown to associate with erbB2 on the surface of breast carcinoma cells, and this interaction appears to facilitate activation of PI3K and invasion (18, 19).

More recently, it was argued that $\alpha_6\beta_4$ functions as an essential adaptor protein for the Met receptor in invasive carcinoma cells (1). The impact of this finding is amplified by the fact that substantial evidence exists for the importance of Met in the scattering, invasion, and metastasis of tumor cells (20, 21). If $\alpha_6\beta_4$ were an essential, specific adaptor for Met function in these events, the consequences for carcinoma biology and therapy would be profound. The potential significance of these results prompted us to re-examine the central findings of this study, which were that a selective physical association between Met and $\alpha_6\beta_4$ exists on the surface of invasive carcinoma cells and that Met cannot promote invasion in the absence of $\alpha_6\beta_4$ expression.

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Met and αβ4 Promote Carcinoma Invasion Independently

EXPERIMENTAL PROCEDURES

Cells—MDA-MB-231 and MDA-MB-435 breast carcinoma cells were obtained from the Lombardi Breast Cancer Depository at Georgetown University Medical Center, DC, and A431 cells were purchased from the American Type Culture Collection. Cells were grown in low glucose Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum, 1% penicillin-streptomycin, and 25 mM HEPES. The generation of stable transfectants of MDA-MB-435 cells that express the αβ4 integrin has been described previously (7). For Met expression studies, a vesicular stomatitis virus (VSV)-expressed retrovirus containing Met cDNA was derived from Dr. Morag Park (McGill University, Montreal, Quebec, Canada). SUM-159 cells were obtained from Dr. Stephen Ethier at the University of Michigan Comprehensive Cancer Center (Ann Arbor, MI) and maintained in Ham’s F-12 medium containing 5% fetal bovine serum, 5 μg/ml insulin, 1 mg/ml hydrocortisone, 1% penicillin-streptomycin, and 25 mM HEPES (22).

To create β4 siRNA-pSUPER and β4 SCR-pSUPER expression vectors, the following oligonucleotides (Invitrogen) were annealed and ligated into pSUPER (a gift from R. Agami, The Netherlands Cancer Institute, Amsterdam, The Netherlands) between the BglII and HindIII sites: β4 siRNA, 5′-gatccgccggagcagtgtgtgctcttcaagagataacacactccggatcatctggagacagtgcgatgtctttctgttgaaggg-3′ and 5′-agtttttttttttttttgtttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttttt
cells induces their ability to invade toward HGF (1). Although our results confirm the observation that expression of the $\alpha_\beta_4$ integrin increases the invasion of these cells toward HGF, we observed that the mock transfectants, which lack $\alpha_\beta_4$, exhibited significant migration toward HGF (Fig. 3A). Moreover, the level of invasion induced by expression of $\alpha_\beta_4$ is comparable with the increased invasion that results from increased Met expression and that this latter mode of invasion occurs in the absence of $\alpha_\beta_4$ (Fig. 2D). Furthermore, expression of $\alpha_\beta_4$ in MDA-MB-435 cells also enhanced the ability of the MDA-MB-435 cells to invade toward other chemoattractants such as lysophosphatidic acid, and this invasion was not inhibited by a function-blocking Met antibody (Fig. 3B). This latter result indicated that the expression of $\alpha_\beta_4$ can enhance the ability of MDA-MB-435 cells to invade independently of Met expression. Invasion assays were performed for 4 h in serum-free medium, and, under these conditions, no significant increase in apoptosis was observed for any cell population as assessed by annexin-V fluorescein isothiocyanate staining (data not shown).

To assess the putative functional dependence of Met on the $\alpha_\beta_4$ integrin from a different perspective, we used SUM-159 cells (22). These invasive breast carcinoma cells express both $\alpha_\beta_4$ and Met (Fig. 4A). Using this cell line, we generated a SUM-159 cell line deficient in $\beta_4$ integrin expression using siRNA strategies (23). Stable infectants that exhibited a reduction in $\beta_4$ expression were sorted by fluorescence-activated cell sorter using a $\beta_4$-specific antibody, and a population of cells was isolated that exhibited no detectable $\beta_4$ expression as evident by immunoblotting (Fig. 4A). Notably, the loss of $\beta_4$ expression had no effect on Met expression in these cells (Fig. 4A). SUM-159 cells exhibited a robust invasion toward HGF (Fig. 4B, C).

**A. Blot:**

![Image](http://www.jbc.org/)

**B. Blot:**

![Image](http://www.jbc.org/)

Fig. 2. Lack of evidence for a constitutive association between Met and the $\alpha_\beta_4$ integrin. A, extracts from the indicated cell lines were immunoprecipitated (IP) with antibodies against Met (clone C-12), $\beta_4$ integrin (clone 439-9B), or the indicated IgG control (rIgG, rabbit IgG; lIgG, rat IgG). Immunoblot analysis of these immunoprecipitates was performed using anti-Met (clone C-12) and anti-$\beta_4$ integrin polyclonal (505) antibodies. B, extracts from A431 cells were immunoprecipitated with $\beta_4$ integrin-specific antibodies (mouse monoclonal clone DO-24 and rabbit polyclonal clone C-12) or IgG controls (mouse IgG and rat IgG), and immunoprecipitates were analyzed by immunoblotting as described in A.
Loss of $\alpha_6\beta_4$ expression reduced the ability of these cells to invade toward HGF by $\sim 25\%$, but it did not abrogate their invasion (Fig. 4B). Moreover, loss of $\alpha_6\beta_4$ expression also diminished the invasion of SUM-159 cells toward 3T3 cell-conditioned medium by $\sim 30\%$.

**DISCUSSION**

The report that the invasive function of the Met receptor is dependent on a physical association with the $\alpha_6\beta_4$ integrin, which provides a "signaling adaptor function," afforded a compelling model for invasive carcinoma that linked these two receptors (1). The data obtained in our study unfortunately do not support the central tenets of this model. Rather, our data argue that the invasive function of Met can be independent of $\alpha_6\beta_4$ and that $\alpha_6\beta_4$ has a generic influence on the invasion of carcinoma cells that is not specific for HGF-dependent invasion.

The demonstration of a physical association between an integrin and a growth factor receptor provides *prima facie* evidence for cooperativeness of function. For this reason, the previous finding that Met and $\alpha_6\beta_4$ could be co-immunoprecipitated from GTL-16 cells, which overexpress a constitutively active form of Met, from COS cells engineered to express both

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**Fig. 2.** *Met can function independently of the $\alpha_6\beta_4$ integrin in MDA-MB-435 cells.* A and B, MDA-MB-435 mock and Met infectants and A431 cells were extracted, and equal amounts of protein extracts were analyzed by immunoblot analysis using Met (clone C-12), $\beta_4$ (clone 505), and actin-specific antibodies. C, MDA-MB-435 mock and Met infectants were extracted at the designated time points during HGF treatment, and extracts were immunoprecipitated (IP) with anti-Met antibody (clone C-12). Immunoblotting was performed with either an anti-Met antibody (*upper panel*, clone C-12) or an anti-pTyr antibody (*lower panel*, clone p-Y-100). D, the ability of MDA-MB-435 mock and Met transfectants to invade Matrigel toward HGF was investigated in a 4-h assay. Prior to these assays, cells were incubated for 30 min with either a control IgG ($-\$) or a Met-specific antibody (clone 95309). The mean number of invasive cells (± S.D.) from five independent fields/well is indicated on the y axis. Similar data were obtained in five separate experiments.
receptors at high levels and from A431 cells, which also express both receptors, strengthened the possibility of a functional dependence (1). Despite using three different carcinoma cell lines that express both Met and $\alpha_9\beta_4$ (A431, MDA-MB-231, and MDA-MB-435, engineered to express $\alpha_9\beta_4$), however, we were unable to detect any evidence for the constitutive association of these receptors by co-immunoprecipitation. The reason for the difference between our results and those of Trusolino et al. (1) is unclear. It is worth noting, however, that in the previous study co-immunoprecipitation data were not provided for either MDA-MB-231 cells or MDA-MB-435/$\alpha_9\beta_4$ cells, and an association between Met and $\alpha_9\beta_4$ in A431 cells was detected only by immunoprecipitation with a $\beta_4$ integrin antibody and immunoblotting with a Met Ab and not vice versa. In addition, the use of another purified $\beta_4$ integrin Ab (439-9B) failed to co-immunoprecipitate Met. Although our data refute the existence of a constitutive association of Met with $\alpha_9\beta_4$ in carcinoma cells, they do not exclude the occurrence of a transient association between these two receptors in certain physiological situations or the possibility that a spurious association may occur on their gross overexpression.

The lack of evidence for a physical association between $\alpha_9\beta_4$ and Met does not negate the possibility that they exhibit functional cooperativity. To evaluate the hypothesis that the invasive function of Met depends on $\alpha_9\beta_4$, we assessed the invasion of MDA-MB-435 cells, which express Met but not $\alpha_9\beta_4$. These cells exhibited significant invasion toward HGF, and their rate of invasion increased in response to increasing Met expression by retroviral infection. The fact that these cells are capable of significant HGF-dependent invasion in the absence of $\alpha_9\beta_4$ expression argues against the necessity of this integrin for Met function. Moreover, a key finding in the pre-

**Fig. 3.** Expression of $\alpha_9\beta_4$ integrin enhances invasion toward multiple growth factors. The ability of MDA-MB-435 mock and $\beta_4$ integrin transfectants to invade Matrigel toward HGF (25 ng/ml) (A) or lysophosphatidic acid (100 nM) (B) was investigated in a 4-h assay. Prior to these assays, cells were incubated for 30 min with either a control IgG (–) or a Met-specific Ab (clone 95309). The mean number of invasive cells (± S.D.) from five independent fields/well is indicated on the $y$ axis. Similar data were obtained in three separate experiments.
vious study was that expression of $\alpha_6\beta_4$ in MDA-MB-435 cells induced their ability to invade toward HGF but not toward EGF. We note, however, EGF is not a suitable negative control because MDA-MB-435 cells lack expression of the EGF receptor (24). Additional support for the hypothesis that the invasive function of Met can occur independently of $\alpha_6\beta_4$ is provided by our data on SUM-159 breast carcinoma cells. These invasive cells express both Met and $\alpha_6\beta_4$, and they exhibit a robust invasion toward HGF. Our finding that elimination of $\alpha_6\beta_4$ expression using a $\beta_4$-specific siRNA reduced but did not abrogate invasive activity toward HGF, however, argues against the conclusion that $\alpha_6\beta_4$ is an essential adaptor for Met in promoting carcinoma invasion. The strength of the SUM-159 data, in contrast to MDA-MB-435 cells, is that this cell line exhibits endogenous expression of both receptors, and the assumption can made that if Met function were dependent on $\alpha_6\beta_4$, it should be evident in such a cell line.

Based on several studies as well as the findings reported here, a consensus is emerging that $\alpha_6\beta_4$ cooperates with growth factor receptors to promote carcinoma invasion and other functions (7, 18, 25). Perhaps the most conclusive evidence in this regard is the finding that macrophage-stimulating protein on binding to its receptor, the Ron tyrosine kinase, promotes an association between Ron and $\alpha_6\beta_4$ that results in PI3K activation and consequent migration (4). There is also evidence that $\alpha_6\beta_4$ can cooperate with erbB2 in breast carcinoma cells to
activate PI3K and promote invasion (18). The conclusion that the function of one specific growth factor receptor (Met) is absolutely dependent on α5β4 for promoting invasion, however, is not supported by our data. A more appropriate assessment of the relationship between Met and α5β4 would be that expression of α5β4 can enhance invasion toward several growth factors, including HGF and lysophosphatidic acid, as well as those present in 3T3 cell-conditioned medium (Figs. 3 and 4). At the same time, our results indicate that the ability of Met to promote invasion is not dependent on α5β4 in these cells and that increasing Met expression in the absence of α5β4 enhances HGF-mediated invasion.

The mechanism that underlies the ability of α5β4 to promote invasion likely involves its ability to stimulate PI3K. Compelling evidence exists for α5β4-mediated activation of this enzyme by mechanisms that include phosphorylation of insulin receptor substrate proteins (26), cooperation with erbB2 (18, 19) and Ron (4), and the elaboration of vascular endothelial growth factor autocrine signaling (27). In addition, the regulated expression of specific transcription factors such as nuclear factor κB (NF-κB) (28) may contribute to the invasive phenotype (28). Clearly, Met is one of several growth factor receptors with a function that may be enhanced by α5β4 expression but that can signal and promote invasion in the absence of α5β4 expression. The challenge ahead is to define the mechanisms by which expression of α5β4 enhances the function of multiple growth factor receptors.

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