

Laminin-induced signaling in tumor cells

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Abstract

Laminin is the main non-collagenous glycoprotein found in the basement membrane. The various laminin isoforms are involved in many physiological and pathological processes, including cancer dissemination. The interaction of cancer cells with laminin was identified as a key event in tumor invasion and metastasis. Laminin effects are mediated by laminin receptors that are divided into two groups: integrin and non-integrin receptors. Activation of a specific signal transduction pathway in the cell depends on various factors and may be altered when normal tissue becomes neoplastic. Laminin signals via multiple signal transduction pathways involving various components such as G-proteins, intracellular calcium, phospholipase D, mitogen activated protein kinases, phosphatases, focal adhesion kinase, small GTPases of the Rho family, and cytoskeleton components. This review focuses on the role of laminin in tumor progression, its signaling via the non-integrin 67kD laminin receptor and via integrins and the reciprocal relations between these receptors in certain tumors.

1. Laminin

Laminin is the main non-collagenous glycoprotein found in the basement membrane [1]. It is a heterotrimer of three subunits, α , β and γ held together by disulphide bonds to form a shape of a cross [2-4]. Five α chains, three β chains and three γ chains have been identified and by combination they assemble to form over 14 laminin

isoforms [5] that have different tissue distributions and development functions [2, 4] (table 1 [5-6]). Laminin is the first basement membrane component appearing during the early stages of embryonic development, and displays a remarkable repertoire of biological functions [6-7]. Laminin is essential for basement membrane assembly [3], promotes cell attachment [3-4, 8] and angiogenesis [4, 9-10], induces neurite outgrowth [3, 11-12], affects gene expression [13-16] and is involved in cell proliferation [4, 15], migration [4, 17-18] and differentiation [3, 6, 19]. Biochemical dissection related some of the laminin functions to specific parts of the glycoprotein. It appears that different parts in the molecule have different effects on cells. Some of these parts are cryptic and interact with cells only after cleavage of laminin by proteases [2, 4, 8]. In vitro, most structural and functional studies have been performed with laminin-1 ($\alpha1\beta1\gamma1$), the main component of Matrigel, which is an extract of basement membrane derived from a murine tumor, and its components are identical, both chemically and immunologically, to authentic basement membrane components [4-5]. Laminin-1 appears early during epithelial morphogenesis in most tissues of the embryo, and remains present as a major epithelial laminin in some adult tissues [6]. Data from studies with laminin-1 cannot be applied to all cell types and all laminin isoforms, and until recently, when recombinant laminin domain production began, the difficulty in isolating intact laminin isoforms precluded the studies of biological functions of most laminin isoforms [5].

Table 1: Laminin isoforms^a.

Name	Chain composition
Laminin-1	$\alpha1\beta1\gamma1$
Laminin-2	$\alpha2\beta1\gamma1$
Laminin-3	$\alpha1\beta2\gamma1$
Laminin-4	$\alpha2\beta2\gamma1$
Laminin-5	$\alpha3\beta3\gamma2$
Laminin-6	$\alpha3\beta1\gamma1$
Laminin-7	$\alpha3\beta2\gamma1$
Laminin-8	$\alpha4\beta1\gamma1$
Laminin-9	$\alpha4\beta2\gamma1$
Laminin-10	$\alpha5\beta1\gamma1$
Laminin-11	$\alpha5\beta2\gamma1$
Laminin-12	$\alpha2\beta1\gamma3$
Laminin-14	$\alpha4\beta2\gamma3$
Laminin-15	$\alpha5\beta2\gamma3$

(a) Based on refs. 5-6.

2. Laminin promotes tumor progression

Metastatic spread of cancer continues to be the greatest challenge to cancer cure. At the core of the process lie the changing adhesive preferences of the tumor cells, which determine their interactions with other cells and with the extracellular matrices, mainly in attachment and degradation processes [3, 20-21]. Basement membranes are lost or

penetrated by tumor cells during invasion and metastasis, and discontinuities were shown in basement membranes of malignant tumors but not in those of their benign counterparts [22]. Therefore, laminin-cell interaction in tumors is different from that of normal tissue [6]. In general, epithelial tumors display a laminin chain composition similar to that of their tissue of origin [5], but the expression of laminin receptors is altered in cancer [5, 23]. The interaction of cancer cells with laminin was identified as a key event in tumor invasion and metastasis [3-4, 21, 24]. Invading tumor cells attach to laminin and the interaction increases the metastatic potential of tumor cells [3-4]. In tumors, laminin is produced by cells in the extracellular matrix, and by tumor cells [25-27]. Laminin promotes tumor dissemination by several mechanisms. One of the mechanisms by which laminin contributes to the metastatic spread is induction of tumor cell proliferation [4, 6]. Laminin-1-adherent cells showed increased proliferative activity and reduced apoptosis in comparison with the laminin-1-nonadherent cells [28]. In addition, it was shown that laminin is chemotactic and haptotactic for tumor cells [17], therefore involved in tumor cell migration [5]. Furthermore, laminin promotes tumor cell invasion by induction of proteases that degrade various components of the extracellular matrix [4]. In certain metastatic cells, but not in normal cells, laminin induces an increase in matrix metalloproteinase-2 (MMP-2) activity [14], which has a key role in invasion and metastasis [29-30]. Indirectly, laminin and more than 20 peptides derived from the glycoprotein contribute to tumor dissemination by promoting angiogenesis [4-5]. The role of the different laminin isoforms in tumor invasion, angiogenesis and metastasis was reviewed by Patarroyo et al. [5]. It was found that laminin peptides have different malignant properties [31]. For example, the YIGSR sequence of the β 1 chain in laminin-1 promotes tumor cell attachment and migration, and when injected together with melanoma cells into a mouse, it decreases angiogenesis, tumor growth and metastasis. Another sequence, SIKVAV, of α 1 chain increases angiogenesis, tumor growth and metastasis when injected together with melanoma cells into a mouse [4, 9, 31].

3. Laminin signaling

It appears that laminin activates various signal transduction pathways. It was shown that chemotaxis induced by laminin-1 is sensitive to pertussis toxin, indicating the involvement of pertussis toxin-sensitive G protein in the signals initiating motility to soluble laminin-1. The absence of response to pertussis toxin indicates that a distinct signal transduction pathway may be involved in haptotaxis [17]. It was shown that human osteoclast-like cells selectively recognize laminin isoforms, an event that induces migration and activates Ca^{2+} -mediated signals. The cell lines adhered to laminin-2 but not to laminin-1, and a sharp increase in intracellular Ca^{2+} was detected upon addition of soluble laminin-2 but not laminin-1, due to release from intracellular calcium stores [18]. Another study showed that laminin-1 induced a rapid and transient mRNA expression of c-fos and c-Jun in PC12 cells, and stimulated the DNA binding activity of the complex of these proteins to the AP-1 site. A correlation was found between cell growth, c-fos expression and the ability of cells to attach to laminin [15]. In tumor cells, laminin-1 results in a time- and dose-dependent activation of phospholipase D (PLD) followed by generation of phosphatidic acid that is involved in signal transduction events leading to the induction of MMP-2 and enhanced invasiveness of metastatic tumor cells [14]. Laminin signaling has been shown to involve kinase/phosphatase cascades since bound

laminin induces protein dephosphorylation in neural cells during process formation [11]. A recent study performed in our laboratory showed that mitogen activated protein kinases (MAPK) are involved in laminin signaling [32]. MAPK cascades transduce a diverse spectrum of extracellular and intracellular stimuli into alterations in gene expression and cellular function. The three major mammalian MAPK subgroups include extracellular signal-regulated kinases (ERKs), c-Jun NH₂-terminal protein kinase/stress-activated protein kinase (JNKs/SAPKs) and p38 MAPK [33-34]. We demonstrated that addition of exogenous soluble laminin-1 results in a significant decrease in the phosphorylation (activation) of ERK, JNK and p38 after 30 minutes of incubation. This laminin-induced dephosphorylation of all MAPK was dose-dependent and transient, as the effect was not seen with other incubation times [32]. Another study demonstrated that incubation of macrophages with a peptide from the laminin- α 1 chain, but not intact laminin-1, triggers protein kinase C-dependent activation of ERK1/2, leading to up-regulation of proteinase expression [35]. These studies suggest that laminin, as an intact glycoprotein, may be involved in signal transduction pathways different than its cleavage products. In addition, various signal transduction pathways may be activated by different laminin receptors.

4. Laminin receptors

The biological effects of laminin are mediated by laminin receptors that are divided into two major groups: integrin and non-integrin receptors (table 2 [5, 21, 36-39]). Insufficient data exist regarding the roles of both families of receptors in mediating the various effects of laminin [2, 23].

Table 2: Laminin receptors and their additional ligands^{a,b}

Receptor	Ligands	
Integrins	α 1 β 1	collagen (I,II,IV), laminin (1, 2)
	α 2 β 1	collagen (I,II,IV), laminin (1, 2), chondroadherin
	α 3 β 1	fibronectin, collagen (I), laminin (2, 5, 8, 10, 11), nidogen, epiligrin, perlecan
	α 6 β 1	laminin (1, 2, 5, 8, 10, 11)
	α 6 β 4	laminin (1, 2, 5, 10)
	α 7 β 1	laminin (1, 2, 8, 10)
	67kD laminin receptor	laminin ^c
Dystroglycan	laminin (1, 2), agrin, perlecan	
Heparan sulphate	laminin (1, 2), collagen XVIII	

(a) Based on refs. 5, 21, 36-39.

(b) Laminin-4 receptor interactions presumed to be similar to those of Laminin-2.

(c) Most studies on Laminin-1.

4.1. 67kD laminin receptor

The 67kD laminin receptor is a non-integrin receptor [21]. A highly conserved 37kD protein is the precursor of the receptor [40-41], but the exact manner by which it configures its mature form is not clear. It was suggested that acylation followed by homo- or heterodimerization of the acylated 37kD precursor, by non-covalent bonds, forms the mature 67kD laminin receptor [41-42]. The amino acid sequence of the 37kD precursor is

extremely well conserved through evolution and corresponds to that of additional proteins, suggesting a multifunctional protein [21, 43]. The cDNA of the 37kD precursor is virtually identical to a cDNA encoding the ribosomal protein p40, suggesting that the protein is a component of the translational machinery [43]. In addition, the 37kD precursor acts as a receptor for cellular prion protein and involved in the life cycle of prions [44-45]. It has also been found that the 37kD precursor is identical to the oncofetal antigen protein that is expressed by tumors [46].

Two laminin binding sites were identified on the 67kD laminin receptor [21]. The first is called G peptide (amino acids 161-180) [47-49], and the second is at the carboxy terminal (amino acids 205-229), and binds to the peptide YIGSR on β 1 chain of laminin [50-51]. The 67kD laminin receptor therefore recognizes various binding sites on laminin that are different from the sites recognized by integrins [21, 48, 50, 52], allowing for higher overall binding affinity, but also a range of binding and signaling options.

4.1.1. Physiological and pathological roles

The 67kD laminin receptor mediates cell attachment to laminin [21, 53]. Co-localization of the 67kD laminin receptor with the cytoskeleton constituents alpha-actinin and vinculin [54] and the focal adhesion plaque [55] was found. The receptor is involved in several physiological processes such as implantation [56], invasive phenotype of trophoblastic tissue [57], angiogenesis [58-59], T-cell biology [52] and shear stress-dependent endothelial nitric oxide synthase expression [51]. 67kD laminin receptor expression is decreased during cell differentiation [21, 23, 60]. Cell contact expression inhibition [59] and p53-dependent down-regulation [61] were also reported. Increased expression of the 67kD laminin receptor correlates with cell proliferation [58], migration [62] and invasion capacity [57]. Clinical data suggest a correlation between 67kD laminin receptor expression in tumor cells and tumor progression. Expression of the receptor has been shown to be up-regulated in neoplastic cells compared to their normal counterparts and directly correlates with an enhanced invasive and metastatic potential in numerous malignancies [23, 63-65]. The receptor has been implicated in laminin-induced tumor cell attachment [52, 63, 66] and migration [67], as well as in tumor angiogenesis [68], growth, invasion and metastasis [21, 63, 66].

4.1.2. 67kD laminin receptor signaling

Studies of laminin-induced signal transduction have focused on integrins [5, 69-70] and provided only limited data regarding the role of the 67kD laminin receptor in signaling. It was shown that a YIGSR-containing peptide and an anti-67kD laminin receptor antibody induce a similar pattern of tyrosine phosphorylation of currently unidentified proteins with a molecular mass ranging from 115 to 130kD and an additional heterogeneous protein group of 32kD [16]. Although the 67kD laminin receptor binds YIGSR [50-51], other laminin-binding sites exist on the receptor [48, 52], and displacement and cross-linking studies showed that other proteins may bind the YIGSR peptide [16].

A recent study in our laboratory focused on the role of the 67kD laminin receptor in laminin signaling, using cells expressing different levels of the receptor [32]. By stable transfection of A375SM melanoma cells, we established lines expressing reduced or elevated 67kD laminin receptor. The antisense-transfected cells that expressed reduced

67kD laminin receptor demonstrated significantly less aggressive tumor phenotype, as reflected by their reduced invasiveness through Matrigel, diminished attachment to laminin and decreased MMP-2 expression and activity [32].

We subsequently analyzed the involvement of the mitogen-activated protein kinases (MAPK) and dual specificity phosphatases (DUSP) in 67kD laminin receptor signaling [32]. MAPK are activated by phosphorylation of tyrosine and threonine in the activation loop and can be inactivated by serine/threonine phosphatases, tyrosine phosphatases and DUSPs [33, 71-72]. We found that the basal phosphorylation extent (activity) of ERK, JNK and p38 was significantly higher in cell lines expressing reduced 67kD laminin receptor, compared to parental cells and sense-transfected cells, regardless of the exposure to exogenous laminin-1. The addition of exogenous soluble laminin-1 resulted in an additional transient significant decrease in the phosphorylation of ERK, JNK and p38. This soluble laminin-induced dephosphorylation of all MAPK was independent of the 67kD laminin receptor level, since it was seen in all cell lines irrespective of the expression level of the receptor. These findings suggest that the 67kD laminin receptor induces prolonged dephosphorylation of ERK, JNK and p38, and that additional exogenous soluble laminin-1 induces further temporary dephosphorylation, apparently not via the 67kD laminin receptor. Further study focused on the DUSPs, MKP-1, PAC-1, MKP-4 and MKP-5, which were found to be expressed by the human A375SM melanoma cell line. We found that the increase in MAPK phosphorylation in cells expressing reduced 67kD laminin receptor is accompanied by a significant reduction in MKP-1 mRNA level and a significant increase in PAC-1 mRNA level, with no change in MKP-4 and MKP-5 mRNA levels [32]. Since prolonged activation of MAPK results in translocation of the activated kinases into the nucleus [33, 71], and since MKP-1 and PAC-1 are nuclear enzymes that are regulated on the transcriptional level [71-74], it is reasonable to speculate that the increase that was seen in the phosphorylation of these MAPK in cells expressing reduced 67kD laminin receptor is related to decreased activity of MKP-1 [32]. The increase in PAC-1 mRNA level that accompanied the increase in the phosphorylation of ERK, JNK and p38 in cells expressing reduced 67kD laminin receptor can be explained as a negative feedback mechanism, since it has been shown that an increase in ERK phosphorylation results in transcription followed by increased activity of PAC-1, that in turn dephosphorylates and inactivates ERK [74-75]. In summary, the 67kD laminin receptor induces down-regulation of MKP-1 expression, that may contribute to the reduced activity (dephosphorylation) of MAPK induced by the receptor, that is followed by an upregulation of PAC-1 expression, as a negative feedback [32]. Interestingly, lower MAPK activity induced by the 67kD laminin receptor in our in vitro model, which was characteristic of aggressive phenotype of the tumor cells [32], correlates with our results in a study of clinical specimens from ovarian carcinoma patients. We found that increased level and activity of all three MAPK families in ovarian carcinoma cells in effusions is associated with clinical parameters of improved outcome and significantly longer overall survival [76].

4.2. Integrins

Integrins are a large family of cell receptors for extracellular matrix proteins and ligands on other cells (table 2). Integrins are heterodimeric combination of various α -subunits with various β -subunits [2, 39]. By having multiple integrins as receptors for

common extracellular matrix proteins, cells have the flexibility to interact with different affinities at the same ligand site and at different sites within the same ligand. The ligand specificity for different integrins can be altered depending on the type of divalent cation present, the surrounding lipid environment and various cell-specific factors. Inside the cell, the short cytoplasmic domains of integrins associate with various cytoskeletal proteins that mediate integrin signal transduction [39]. At least eight integrins bind laminin; some of them bind additional extracellular matrix components as well, and cellular response depends on the sum of integrin-extracellular matrix interactions [2]. Integrins recognize mainly laminin α chains and hence determine cell adhesion and response to laminin isoforms. Although some functions may be common to all laminin variants, other may be unique and isoform-specific, depending on the tissue or organ in which they are abundant [5].

4.2.1. Integrin signaling

Although it is clear that integrins transduce signals across the plasma membrane that affect gene expression, limited data exist regarding the specific signal transduction pathways activated by specific ligands [39, 69]. There are two types of integrin-related signal transduction. The first is direct signaling, where stimulation of integrins by extracellular proteins triggers intracellular signaling events. The second is integrin modulation of mitogen signaling; in this case, integrin-mediated cell anchorage influences signaling pathways activated by growth factors [70]. In general, integrin direct signaling activates focal adhesion kinase (FAK), small GTPases of the Rho family, and MAPK [70, 77-78], resulting in accumulation of highly phosphorylated proteins and cytoskeletal molecules at adhesion sites [79-80]. Integrin clustering causes activation and autophosphorylation of FAK, which is a cytoplasmic tyrosine kinase. Tyrosine-phosphorylated FAK can recruit Src-family kinases to focal contact sites. This sets up additional tyrosine phosphorylation of proteins such as cytoskeletal proteins and adaptor proteins such as Grb2 [70, 78, 81]. Small GTPases of the Rho family (Rho, Rac and Cdc42) are involved in integrin signal transduction and affect cytoskeleton arrangement. Rho contributes to cell adhesion to extracellular matrix. Rac and Cdc42, via phosphoinositide 3 kinase (PI3K), mediate the increase in cell motility and invasiveness induced by the integrin [82-83]. Some integrins activate MAPK cascades [80, 84]. For example, laminin binding to the integrin $\alpha 6\beta 4$ results in activation of an associated kinase and consequently tyrosine phosphorylation of the $\beta 4$ subunit cytoplasmic domain, followed by association of the adaptor protein Shc with tyrosine phosphorylated $\beta 4$ integrin subunit. Shc is then phosphorylated on tyrosine residues, presumably by an integrin-associated kinase, and combines with the adaptor protein Grb2, which exists in a complex with the ras GTP exchange factor SOS. This leads to Ras activation followed by activation of a kinase cascade consisting of Raf, MEK (MAPK/ERK kinase) and ERK, resulting in increased cell motility and proliferation [69, 84]. In addition, integrin $\alpha 6\beta 4$ activates the JNK cascade, via Rac1, resulting in jun protein expression. Jun associates with fos, whose expression is induced by ERK cascade, to form the AP-1 transcription factor [84]. In human hepatocellular carcinoma cells, laminin-binding integrin $\alpha 6\beta 1$ stimulation resulted in FAK tyrosine phosphorylation, leading to FAK-GRB2 association and ERK cascade activation, which promotes tumor cell migration [85]. Interestingly, aggregation of integrin receptors, even in the absence of ligand occupancy, is sufficient to

induce a prompt trans-membrane accumulation of at least 20 signal transduction molecules, including Src, Rho, Rac1, Ras, Erk1/2 and JNK. Thus, integrin aggregation with or without ligand occupancy triggers activation of both ERK and JNK cascades [80].

4.3. 67kD laminin receptor and integrins

Integrins and the 67kD laminin receptor act together in transducing laminin effects. Limited data exist regarding the roles of the different receptors in mediating specific laminin effects. There are studies that indicate an association between the 67kD laminin receptor and the $\alpha 6$ integrin subunit, that is a part of the laminin-binding integrins $\alpha 6\beta 4$ and $\alpha 6\beta 1$ [21, 23]. It was found that activation of human T lymphocytes induces an increase in both 67kD laminin receptor and $\alpha 6\beta 1$ integrin expression, and that the two receptors mediate avid cellular adherence to laminin [52]. The 67kD laminin receptor and the $\alpha 6\beta 1$ integrin were shown to be co-expressed and co-regulated in small-cell lung carcinoma cell lines, and their expression correlated with ability to adhere to laminin [86]. An additional study showed increased expression of the $\alpha 6$ integrin subunit and of the 67kD laminin receptor in pancreatic adenocarcinoma specimens, compared with normal pancreatic tissue from the same patient, indicating co-regulation of the receptors [87]. As opposed to the above report, differential expression of the $\alpha 6$ integrin subunit and the 67kD laminin receptor was seen in human hepatocellular carcinoma. Although higher expression of both the $\alpha 6$ integrin subunit and the 67kD laminin receptor was found in tumor specimens compared to normal tissues from the same patient, the increase in $\alpha 6$ integrin subunit expression was more pronounced than that of the 67kD laminin receptor, indicating different regulation of receptor expression [88]. An in vitro study found co-regulation and physical association of the $\alpha 6$ integrin subunit and the 67kD laminin receptor. Following incubation of a human vulvar epidermoid carcinoma cell line with laminin for different time periods, the regulation of the 67kD laminin receptor correlated with expression of the $\alpha 6$ integrin subunit but not with the expression of other laminin receptors, and cytokine treatment resulted in a reduction in the expression of these two receptors [24]. Specific reduction of the $\alpha 6$ integrin subunit by an antisense was accompanied by a proportional decrease in the cell surface expression of the 67kD laminin receptor. Biochemical analyses indicated co-immunoprecipitation of 67kD laminin receptor and $\alpha 6$ integrin subunit [24]. Integrins bind laminin at different sites than the 67kD laminin receptor, which may lead to higher laminin-binding affinity. Some investigators suggested that the 67kD laminin receptor is just a co-factor for laminin-integrin interactions [21, 24, 48], but other reports indicate that the 67kD laminin receptor may have additional functions [44, 88]. The 67kD laminin receptor does not co-localize with $\alpha 6$ integrin subunit in neuroblastoma cell line [44]. Results from an in vitro study and analysis of clinical specimens in our laboratory are in agreement with the hypothesis that the 67kD laminin receptor is not merely a co-factor for laminin-integrin interactions. We found that A375SM melanoma cells express two alternatively spliced isoforms of the $\alpha 6$ integrin subunit, $\alpha 6A$ and $\alpha 6B$. However, cells expressing reduced 67kD laminin receptor showed a significantly reduced mRNA level of the $\alpha 6B$ integrin subunit isoform, with no significant change in $\alpha 6A$ isoform mRNA level. Thus, the $\alpha 6B$ is the important isoform in the concept of co-regulation with the 67kD laminin receptor in the A375SM melanoma cell line [32]. Our study of clinical

material analyzed the expression of the 67kD laminin receptor and the $\alpha 6$ integrin subunit, in effusions and solid tumors of patients diagnosed with serous ovarian carcinoma, and analyzed their predictive roles. 67kD laminin receptor mRNA and protein expression was found to be independent of that of the $\alpha 6$ integrin subunit in both solid tumors and effusions of serous ovarian carcinoma. Expression of the 67kD laminin receptor was detected in the majority of specimens, at all anatomic sites, and did not correlate with clinico-pathological parameters or survival. In contrast, loss of $\alpha 6$ integrin subunit expression predicted better overall survival [89].

Malignant mesothelioma (MM) is one of the most aggressive human cancers, with a median survival of 8 months if untreated, and up to 2 years in recent series, when surgery was combined with adjuvant therapy [90]. With the exception of brain tumors, such as Glioblastoma Multiforme, that are confined to the central nervous system by anatomic structures, no tumor is less susceptible to clinically detectable distant metastasis and still is associated with these mortality figures. This despite the fact that MM is clearly capable of local invasion and displays the integrin profile needed in order to mediate attachment to all major extracellular matrix proteins [91-92]. In a recent study, frequent mRNA, but only rare protein expression of the 67kD laminin receptor was seen in clinical specimens of MM [Reich et al., submitted for publication]. In contrast, expression of this receptor was seen in the majority of breast and lung carcinomas, tumors with high metastatic potential, in addition to the above-described ovarian carcinomas [Reich et al., submitted for publication]. These findings suggest that the differences between MM and carcinomas regarding expression of the 67kD laminin receptor may account at least in part for the reduced ability of MM to metastasize to distant organs, due to lack of the signaling mediated by the receptor. Local invasion and the less frequent distant metastasis in MM may be mediated by the $\alpha 6$ integrin laminin receptor rather than the non-integrin 67kD laminin receptor. Our recent finding that MM shows significantly higher expression of the $\alpha 6$ integrin subunit compared to ovarian and breast carcinomas using flow cytometry [Sigstad et al., submitted for publication] supports this hypothesis.

5. Summary

The interaction of cancer cells with laminin is a key-event in tumor invasion and metastasis. Laminin effects are mediated by laminin receptors, and receptor expression is altered in cancer. Activation of a specific signal transduction pathway in the cell depends on the laminin isoforms the cell binds to, the conformation of the glycoprotein, the duration of exposure to laminin and the expression pattern of the different laminin receptors. All the above factors may be altered when normal tissue becomes neoplastic, resulting in various laminin mediated signaling that promote tumor dissemination.

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